CANAUX IONIQUES

35th Ion Channel Meeting

September 6th-9th, 2026
Domaine du Lazaret, Sète, France



Plenary lecture

Stefan Feske (New York, USA)

When mechanics drives biology

Thomas Grutter (Strasbourg, France)
Medha M. Pathak (California, USA)
Annette Hammes (Berlin, Germany)

Channelopathies & Transporteropathies: rare variants, broad impact

Elena Bossi (Varese, Italy)
László Csanády (Budapest, Hungary)
Michael Pusch (Genova, Italy)

The neglected CRAC Proteins: Orai2, Orai3 and STIM2

Barbara Niemeyer (Saarbrücken, Germany)
Juan A. Rosado (Badajoz, Spain)
Rajender K. Motiani (Delhi-NCR, India)

Intracellular ion channels in health and diseases

Irina Serysheva (Houston, USA)
Andrea Guse (Hamburg, Germany)
Christian Grimm (Munich, Germany)

Adaptation: how ion channels enable cells to detect changes

Qiang Liu (Hong Kong, Hong Kong)
Lina Maria Jaime Tobon (Montpellier, France)

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ORGANIZING AND SCIENTIFIC COMMITTEES

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

Alban GIRAULT (chair)
CRCLille, Equipe Pancrest, UMR9020 CNRS - U1366 Inserm, Université de Picardie Jules Verne
alban.girault@u-picardie.fr

Loïc LEMONNIER
CRCLille, équipe IonIC, U1366 Inserm, Université de Lille
loic.lemonnier@inserm.fr

Jérôme THIREAU
Laboratoire PhyMedExp, Montpellier
jerome.thireau@inserm.fr

Laetitia MONY
Institut de Biologie, École Normale Supérieure, Paris
laetitia.mony@bio.ens.psl.eu

Barbara RIBEIRO DE OLIVEIRA
Nantes Université, CNRS, INSERM, L'institut du thorax
barbara.ribeiro@univ-nantes.fr

Jean-Sébastien ROUGIER
IBMM, Bern
jean-sebastien.rougier@unibe.ch

Valerio FARFARIELLO
CRCLille, équipe IonIC, U1366 Inserm, Université de Lille
valerio.farfariello@univ-lille.fr

Olga ANDRINI
MeLiS, CNRS UMR 5284, INSERM U1314, Université Lyon 1 Claude Bernard
olga.andrini@univ-lyon1.fr

Bruno CONSTANTIN
IFR Santé, Laboratoire 4CS, Université de Poitiers, CNRS UAR BioS n° 2038
bruno.constantin@univ-poitiers.fr

Rémi PEYRONNET
Institute for Experimental Cardiovascular Medicine, University of Freiburg
remi.peyronnet@uniklinik-freiburg.de

Natacha PREVARSKAYA
CRCLille, équipe IonIC, U1366 Inserm, Université de Lille
natacha.prevarskaya@univ-lille.fr

Joël TABAK
University of Exeter
j.tabak@exeter.ac.uk

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

Alban GIRAULT (Treasurer)
CRCLille, Equipe Pancrest, UMR9020 CNRS - U1366 Inserm, Université de Picardie Jules Verne
alban-girault@u-picardie.fr

Cécile HILAIRE (Deputy Treasurer)
INM INSERM U1298, Université de Montpellier
cecile.hilaire@umontpellier.fr

Jérôme THIREAU (Secretary)
PhyMedExp, CNRS UMR 9214, INSERM U1046, Université de Montpellier
jerome.thireau@inserm.fr

Loïc LEMONNIER (Secretary)
CRCLille, équipe IonIC, U1366 Inserm, Université de Lille
loic.lemonnier@inserm.fr

THE EUROPEAN CALCIUM SOCIETY

Dear meeting participant,

*It's my pleasure to introduce the **(junior) European Calcium Society (ECS/jECS).** The ECS, including jECS, is an international non-profit scientific society dedicated to promoting research and collaboration in the field of Ca^{2+} binding, Ca^{2+} signalling, and the molecular and cellular components that constitute the broader "Ca^{2+} toolkit". Founded in 1997, ECS has grown into a vibrant and inclusive community of researchers spanning Europe and beyond, with more than 200 members from over 30 countries. The Society aims to connect scientists across disciplines, geographical regions, and career stages, fostering exchange between active researchers in the calcium field.*

A central activity of ECS is the organization and support of high-quality scientific meetings, including the biennial International Meetings of the European Calcium Society, focused/thematic symposia, webinars, and ECS-supported sessions at complementary scientific conferences such as this Ion Channel meeting! These activities provide a forum for presenting cutting-edge discoveries, discussing new technologies and concepts, and strengthening collaborations across the Ca^{2+} research community. Through its meetings and workshops, ECS actively supports the visibility and development of the Ca^{2+} field, covering topics ranging from fundamental mechanisms of Ca^{2+} signalling to its roles in physiology, disease, and therapeutic innovation.

ECS places particular emphasis on supporting early career researchers and ensuring their active participation in the Society. This commitment is reflected in travel fellowships, reduced membership and registration fees, poster prizes, dedicated junior ECS activities, and the establishment of the junior ECS Board, which gives early career scientists a direct voice in shaping Society initiatives. ECS fellowships help young researchers attend ECS events, present their work, build networks, and engage with leaders in the field. In addition to this, special attention is given to researchers from emerging countries, who are supported with dedicated travel fellowships to attend ECS meetings.

Through these activities, ECS continues to serve as a welcoming, international, and scientifically rigorous platform for the Ca^{2+} signalling community. By combining excellent science with strong support for symposia, networking, training, and early career development, the Society contributes to the continued growth, visibility, and renewal of the Ca^{2+} research field.

We hope to welcome new ECS memberships, which help us to further develop the Society. Becoming a member of ECS can be easily done online via https://calciumsociety.com/ with special multi-year membership options and a special 5-year deal for PhD students.

Kind regards,

Geert Bultynck

Secretary General of the ECS

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We are very grateful to the following sponsors
for their financial and material support.

FOREWORDS/AVANT-PROPOS

Dear colleagues,

It is a pleasure to welcome you once again to Sète at the Domaine du Lazaret for the 35th Ion Channels Meeting. This year, we are pleased to partner with the European Calcium Society (ECS) to once again present a rich and varied program. Through the various sessions, we will have the opportunity to explore the latest advances in both technology and scientific knowledge, ranging from the field of mechanotransduction to ion channel-dependent cellular adaptation, as well as the genetics of rare mutants in pathological contexts. In addition, two ECS symposia dedicated to calcium homeostasis and its dysregulations will allow us to explore the latest advances regarding CRAC channels and proteins involved in store-operated calcium entry in both healthy and pathological contexts. In addition, our young researchers will present a wide range of studies exploring the diversity of channels and transporters across species and their roles in the response to therapies. All of these presentations will highlight the latest findings in the fields of cardiology, muscle and nerve physiology, oncology, and many other fields.

The study of ion channels, regardless of the approach taken, from basic research to clinical studies combining electrophysiology, molecular biology, and AI-assisted techniques, remains a central field in the advancement of knowledge. The French Ion Channels Association is proud to contribute to this progress through the 35th edition of its conference. We are very pleased to welcome 115 participants from all over the world and to have received approximately 70 abstract submissions! Taken together, these factors unequivocally demonstrate the dynamism of our field of research.

This meeting would not be possible without the support of our sponsors and the dedication and hard work of the organizing committee: Valerio Farfariello, Loïc Lemonnier, Laetitia Mony, Barbara Ribeiro, Jean-Sébastien Rougier, Olga Andrini, Rémi Peyronnet, Joël Tabak, Bruno Constantin, Natacha Prevarskaya, and Jérôme Thireau — not to forget Arnaud Monteil and Caroline Strube, the true guardians of the soul of this congress.

We hope that this 35th edition will lead to new and fruitful collaborations through the scientific discussions taking place during the meeting. We also hope that this event will serve as a starting point for our young researchers, opening up new opportunities and connections that will help them build their networks and shape their future careers.

Enjoy the conference!

Cécile and Alban

Presidents of the 35th Ion Channels Meeting

PROGRAM

Sunday, September 6th, 2026

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

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

21:00 Plenary lecture

Pr. Stefan Feske **(New York University Grossman School of Medicine, New York, USA)**
''Novel Ion Channels and Transporters in Immunity''

Monday, September 7th, 2026

08:30 Opening session

08:45 Symposium 1: "When mechanics drives biology"
Organized by Rémi PEYRONNET (Institute for Experimental Cardiovascular Medicine, University of Freiburg, Germany)

Thomas Grutter **(CBST, UMR 7199, Strasbourg, France)**
''Optical control of PIEZO channels provides new insights into mechanogating''
Medha M. Pathak **(UC Irvine, Irvine, CA, USA)**
''Molecular Choreography of Piezo1 in Development and Repair''
Annette Hammes **(Max Delbrück Center for Molecular Medicine, Berlin, Germany)**
''PIEZO2 Mechanotransduction in Coronary Angiogenesis and Endothelial Fate Specification''

Selected speaker:
Thomas Manicom Ramsamy **(Institut for Advanced Biosciences, Grenoble, France)**
''An epigenetic BRG1-P300 module gates mechanosensitive-channel expression and endothelial dysfunction in cerebral cavernous malformations''

10:30 Sponsor presentation

10:45 ***Coffee break***

11:15 Oral communication session 1: "Ion channel/transporter diversity across species"
Organized by Laetitia MONY (Institut de Biologie, École Normale Supérieure, Paris, France)

Sara Kaaki **(Université d'Orléans, Laboratoire Physiologie, Ecologie et Environnement (P2E), UR 1207, USC-INRAE 1328, France)**
''Honeybee α1α8β1 nicotinic acetylcholine receptor generates several distinct stoichiometries associated to acetylcholine activation''

Luca Pigelet **(Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), Sophia Antipolis, France)**
''Species-specific properties of ASICs in human DRG neurons''
Sarah Shoushrah **(Institute for Functional Gene Analytics, Bonn-Rhein-Sieg University of Applied Sciences, Rheinbach, Germany)**
''Do homomeric assemblies of human epithelial sodium channels (ENaC) exist? limitations of the Xenopus laevis oocytes model''
George Parsons **(Biosciences Institute, Newcastle University, UK)**
''Reshaping the binding pocket of APC superfamily solute carriers (SLCS)''

12:15 1-minute oral presentation for posters (even numbers)

12:45 Lunch

14:00 Poster session 1 (even numbers)

15:30 Coffee break

15:45 Sponsor presentation

16:00 Symposium 2: "Channelopathies & Transporteropathies: rare variants, broad impact"
Organized by Olga ANDRINI (MeLiS, CNRS UMR 5284, INSERM U1314, Université Lyon 1 Claude Bernard, France)

Elena Bossi **(Università degli Studi dell'Insubria, Varese, Italy)**
''GABA Homeostasis and Neurodevelopment: How SLC6A1 (GAT1) Mutations Disrupt GABAergic Transmission''
László Csanády **(Semmelweis University, Budapest, Hungary)**
''Molecular pathology of cystic fibrosis associated rare CFTR mutations''
Michael Pusch **(Istituto di Biofisica, CNR, Genova, Italy)**
''Dominant effects of loss- and gain-of-function variants in neuronal endosomal CLC transporters''

Selected speaker:
Alexandra Typou **(Institute of Functional Genomics, Montpellier, France)**
''In vivo characterization of a disease-associated NALCN variant using a conditional knock-in mouse model''

17:45 - 18:45 Oral communication session 2: "Ion channels in cancer: from cellular adaptation to therapeutic response"
Organized by Valerio FARFARIELLO (CRCLille, INSERM U1366, Université de Lille, France)

Juan Manuel Gómez-Sedeño **(Master in Translational Biomedicine. Institute of Medical-Biological Research, Universidad Veracruzana. Agustín de Iturbide S/N. Col. Flores Magón.Veracruz, Veracruz, México)**

''Expression profiling of TRPM2 in colorectal cancer: a combined in silico and ex vivo analysis''
Estefania Torres Ortiz **(Institute of Biology Valrose, Nice, France)**
''membrane depolarization drives WNT/β-catenin signaling in colonic homeostasis and colorectal cancer''
Théo Branchu **(Laboratory Channels and Connexins in Cancer and Cell Stemness, University of Poitiers, France)**
''Carboxyamidotriazole impacts store-operated calcium entries and decreases stem-like properties in glioblastoma stem cells''
Alice Hasselsweiller **(Univ. Lille, Inserm, CHU Lille, CNRS, U1366-UMR9020 – CRCLille – Cancer Research Center of Lille, Lille, France)**
''TRPM2 promotes therapeutic resistance in triple-negative breast cancer through the regulation of intracellular calcium homeostasis''

19:30 Apéritif dînatoire sétois

Tuesday, September 8th, 2026

08:45 Symposium 3: "The neglected CRAC Proteins: Orai2, Orai3 and STIM2"
Organized by Bruno CONSTANTIN (IFR Santé, Laboratoire 4CS, Université de Poitiers, CNRS UAR BioS N° 2038)

Barbara Niemeyer **(Saarland University, Saarbrücken, Germany)**
''STIM2 and Orai and calcium entries''
Juan A. Rosado **(University of Extremadura, Badajoz, Spain)**
''Functional role of Orai3 in the pathophysiology of luminal breast cancer''
Rajender K. Motiani **(UNESCO-Regional Centre for Biotechnology, Delhi-NCR, India)**
''Demystifying the mystery of Orai3 function and regulation in Pancreatic Cancer''

Selected speaker:
Leonie Hoppe **(Molecular Biophysics, Saarland University, Homburg, Germany)**
''STIM2 mutations found in a patient with non-tuberculous mycobacterium infection display altered store-operated Ca^{2+} influx (SOCE)''

10:15 Coffee break

10:30 - 11:00 1-minute oral presentation for posters (odd numbers)

11:00 Coffee break

11:15 - 12:45 Poster Session 2 (odd number)

12:45 Lunch

13:45 Appointment for Social event

17:15 Symposium 4: "Intracellular ion channels in health and diseases"
Organized by Natacha PREVARSKAYA (CRCLille, INSERM U1366, Université de Lille, France)

Irina Serysheva **(McGovern Medical School, Houston, USA)**
''Structural Insights into Isoform-Specific Regulation of IP3 Receptors''
Andrea Guse **(Center for experimental medicine, Institute of Biochemistry and Molecular Cell Biology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany)**
''NAADP evoked Calcium Signaling''
Christian Grimm **(Department of Pharmacology, University of Oxford, Department of Pharmacology, LMU University of Munich Fraunhofer Institute Munich, Germany)**
''Endolysosomal TRPMLs/TPCs: New aspects of their physiological and pathophysiological relevance''

Selected speaker:
Quentin Lelievre **(LP2M, CNRS, Nice, France)**
''Biophysical properties of acid-sensitive twik1 dynamic selectivity: insights into iron metabolism''

19:00 Annual meeting of the Association

20:00 Dinner

21:00 Social Event

Wednesday, September 9th, 2026

09:30 Symposium 5: "Adaptation: how ion channels enable cells to detect changes"
Organized by Joël TABAK (University of Exeter, England)

Qiang Liu **(City University of Hong Kong, Hong Kong)**
''Adaptive Action Potentials and Spike Coding in *C. elegans*''
Lina Maria Jaime Tobon **(INM, Montpellier, France)**
''How the auditory system achieves high dynamic range''

Selected speakers:
Marvin Gaillardon **(Institut de Génomique Fonctionnelle, Montpellier, France)**
''Ionic mechanisms of parasympathetic regulation of heart rate''
Josep Martí-Solans **(Observatoire Océanologique de Banyuls-sur-Mer, CNRS/Sorbonne Université, France)**
''Ion channel-driven voltage dynamics as spatial cues for morphogenesis in ascidians''

11:15 Coffee break

11:40 Prizes and Meeting closure

12:00 Lunch

SYMPOSIA AND ORAL COMMUNICATIONS ABSTRACTS

Sunday, September 6th, 2026

21:00 - Plenary lecture

NOVEL ION CHANNELS AND TRANSPORTERS IN IMMUNITY

Stefan Feske
New York University Grossman School of Medicine, USA.

Research in the Feske lab seeks to define how CRAC channels and Ca2+ signaling pathways regulate immune responses in both health and disease. In recent years, the lab has concentrated on identifying and characterizing novel ion channels and transporters, along with their associated ionic signaling pathways in lymphocytes, that control immune function under physiological and pathological conditions. These include a diverse set of membrane transport proteins for inorganic ions such as calcium, zinc, copper, and chloride, as well as transporters for organic metabolites. This lecture will outline the screening strategies used to discover new membrane transport proteins involved in regulating T and B cell function, it will examine the mechanisms by which they operate and describe human disease phenotypes associated with channelopathies in the immune system. Specific lecture topics will include the regulation of B cell differentiation and humoral immune responses by solute carriers and calcium pumps, as well as the role of zinc transporters in T cell function and immunity to infection.

Monday, September 7th, 2026

08:45 - **Symposium 1: "When mechanics drives biology"**

Organized by Rémi Peyronnet (Institute for Experimental Cardiovascular Medicine, University of Freiburg, Germany)

OPTICAL CONTROL OF PIEZO CHANNELS PROVIDES NEW INSIGHTS INTO MECHANOGATING

Thomas Grutter

University of Strasbourg, CNRS, UMR 7199 CBST, Ion Channel Engineering Team.

PIEZO channels are mechanically activated ion channels expressed in many tissues. They play key roles in mechanotransduction, allowing cells to detect and respond to the mechanical forces they experience daily. Although these channels are naturally activated by mechanical stimuli, specific tools enabling their controlled activation through alternative approaches remain limited. To address this, we have developed light-sensitive chemical tools that enable optical control of PIEZO channels in living cells. This is achieved by covalently attaching an azobenzene-based maleimide photoswitch to an engineered cysteine residue in PIEZO1. Light-induced cis–trans isomerization of the azobenzene induces geometrical changes that directly affect channel gating. We show that engineered PIEZO1 expressed in HEK293T-P1KO and Neuro2A-P1KO cells can be directly activated by UV light when the photoswitch is in its cis state, thereby promoting channel opening. In this lecture, I will present how this approach provides new insights into the molecular mechanisms of PIEZO channel gating.

MOLECULAR CHOREOGRAPHY OF PIEZO1 IN DEVELOPMENT AND REPAIR

Medha Pathak

Department of Physiology & Biophysics, Department of Biomedical Engineering Sue and Bill Gross Stem Cell Research Center.

A central challenge in PIEZO1 biology is understanding how mechanical force is sensed and converted into context-specific cellular responses within the native environment. Visualizing the spatiotemporal dynamics of endogenous PIEZO1 offers a direct route to this understanding. We address this by imaging endogenous PIEZO1 in situ across scales, from single channels to organized human tissue. This approach revealed that PIEZO1 is mobile within the plasma membrane, displays heterogeneous behaviors, and its spatial distribution and temporal dynamics directly influence cell migration, establishing channel localization as a functional variable rather than a structural detail.

To visualize PIEZO1 in human systems at native expression levels, we engineered iPSCs so that endogenous PIEZO1 is tagged with HaloTag, resolving channel localization and activity across diverse cell types and in hiPSC-derived tissue models. The approach achieves temporal resolution approaching that of patch-clamp electrophysiology while allowing non-invasive, multiplexed imaging in native conditions. In hiPSC-derived brain organoids, PIEZO1 localizes

preferentially to mechanically active regions along the apical border and cell-cell junctions, and its loss alters lumen morphology, linking molecular-scale channel behavior to tissue architecture in situ.

Together, our work shows that spatiotemporal dynamics of endogenous PIEZO1 govern cell behavior and tissue organization, and establishes imaging of endogenous, HaloTag-tagged PIEZO1 as a route to study force sensing in situ, from single channels to intact human tissue and disease modeling.

PIEZO2 MECHANOTRANSDUCTION IN CORONARY ANGIOGENESIS AND ENDOTHELIAL FATE SPECIFICATION

Annette Hammes
Max Delbrück Center for Molecular Medicine, Berlin, Germany.

Developing coronary vessels are continuously exposed to mechanical forces, yet how mechanosensitive ion channels direct vascular patterning remains poorly understood. Here, we identify the mechanically activated ion channel PIEZO2 as a context-specific regulator of coronary angiogenesis during heart development. PIEZO2 is transiently expressed in discrete coronary endothelial cell populations during a critical remodelling phase and mediates mechanically activated ionic currents in these cells.

Genetic loss of PIEZO2 in mice, as well as pathogenic human PIEZO2 variants, resulted in aberrant coronary vessel architecture and left ventricular hyperplasia, demonstrating that tightly controlled PIEZO2 activity is required for normal vascular and cardiac morphogenesis. Although PIEZO2 is less broadly expressed than PIEZO1, our findings reveal a non-redundant role for PIEZO2-mediated mechanotransduction in specific angiogenic contexts.

To establish scalable human model systems and dissect underlying pathomechanisms, we combined human induced pluripotent stem cell (hiPSC)-derived endothelial differentiation platforms with primary human umbilical vein endothelial cells (HUVECs). Using PIEZO2-deficient human induced endothelial cells revealed altered transcriptional states, impaired endothelial fate specification, and defective angiogenic behaviour, supporting an essential role for PIEZO2 in angiogenic network formation and endothelial morphogenesis under mechanically regulated conditions.

Beyond PIEZO2 loss-of-function phenotypes, we investigated pathways regulating *PIEZO2* expression. FOXO1 and TGFβ signalling induced *PIEZO2* expression levels, linking PIEZO2 regulation to molecular programmes involved in arterial endothelial fate specification, consistent with the established role of TGFβ signalling in arterial identity. Intriguingly, PIEZO2 expression was already detected in undifferentiated hiPSCs and human H1 embryonic stem cells, suggesting a previously unrecognised role in stem cell biology. Furthermore, we identified a developmental PIEZO2 isoform switch during differentiation from hiPSCs to endothelial cells, indicating dynamic regulation of PIEZO2 isoform usage during endothelial specification.

Together, our findings establish PIEZO2 as a mechanically gated regulator of coronary vascular remodelling and endothelial fate decisions, providing new insight into how force-sensitive ion channels integrate biomechanical and transcriptional signalling during cardiovascular development. These results position PIEZO2 as a potential therapeutic target for modulating angiogenesis and vascular regeneration in cardiovascular disease.

AN EPIGENETIC BRG1–P300 MODULE GATES MECHANOSENSITIVE-CHANNEL EXPRESSION AND ENDOTHELIAL DYSFUNCTION IN CEREBRAL CAVERNOUS MALFORMATIONS.

MANICOM RAMSAMY Thomas[1]; POVEDA VICEDO Cecilia[1]; BOURRIN-REYNARD ingrid[1]; ODDOU christiane[1]; WONG Cassandra[2]; GINGRAS Anne-Claude[2]; FAUROBERT Eva[1]
[1]Institut for Advanced Biosciences.
[2]Lunenfeld-Tanenbaum Research Institute.

Cerebral cavernous malformations (CCM) are vascular lesions of the brain arising from loss-of-function mutations in the *CCM1/KRIT1*, *CCM2* or *CCM3* genes. Strikingly, lesions develop only in low-flow vessels: CCM-deficient endothelial cells (ECs) misinterpret their mechanical environment, behaving as if under high shear stress. They become activated and invasive, indicative of defective mechanosensation and transduction. Whereas mechanoeffectors such as ROCK1/2 and the overexpressed flow-sensitive transcription factors KLF2/KLF4 have been extensively described for their crucial role in this disease, upstream mechanosensors remained unknown. We recently demonstrated that the overexpressed mechanosensitive ion channels (MSCs) PIEZO1, TRPV2 and TRPV4 have complementary causative roles in CCM dysregulated mechanotransduction pathway (see *Faurobert et al.*, submitted abstract).
To understand how these components are wired together, we mapped the protein–protein interaction network (PPIN) of MSCs, ROCK kinases and transcription factors in control versus CCM2-depleted ECs using proximity-labeling proteomics (BioID). In control ECs, MSCs, ROCKs and the KLF/YAP1 transcriptional machinery form an integrated and coherent network in which the CCM1/2 complex bridges cell–cell junctions to Notch, VEGFR2, KLF4 and YAP. Loss of CCM2 rewires this architecture: the junctional module disconnects from the signaling machinery. Notch and Hippo modules are lost. YAP1 becomes the dominant transcriptional coordinator while KLF4 is isolated. Interestingly, a strong chromatin-modifying module appears built around the SWI/SNF ATPase BRG1 and the acetyltransferase p300, sustained by ROCKs.

To confront this reconstructed PPIN to the CCM-related biological processes, we depleted either BRG1 or p300 in CCM2-silenced ECs. Their silencing restored control levels of KLF2/4, PIEZO1, TRPV2 and TRPV4 transcripts. Importantly, their depletion also led to the restoration of the adhesive and transcriptomic defects of CCM2-depleted ECs, confirming the crucial role of these epigenetic factors in the rewiring of this pathological pathway.

Together, these findings identify a chromatin opener and transcriptional activator the BRG1–p300 module as the point where CCM2 loss and abnormal mechanical signaling converge to amplify mechanosensitive-channel expression and destabilize endothelial program. By placing

channel expression under druggable chromatin control, this work nominates BRG1 and p300 as therapeutic targets at the intersection of ion-channel biology, mechanics and chromatin.

11:15 - **Oral communication session 1: "Ion channel/transporter diversity across species"**

Organized by Laetitia MONY (Institut de Biologie, École Normale Supérieure, Paris, France)

HONEYBEE α1α8β1 NICOTINIC ACETYLCHOLINE RECEPTOR GENERATES SEVERAL DISTINCT STOICHIOMETRIES ASSOCIATED TO ACETYLCHOLINE ACTIVATION

Sara Kaaki[1]; Alison Cartereau[1]; Thierry Cens[2]; Pierre Charnet[2]; Daniel Auguin[1]; Emiliane Taillebois[1]; Steeve H. Thany[1]

[1]*Université d'Orléans, Laboratoire Physiologie, Ecologie et Environnement (P2E), UR 1207, USC-INRAE 1328.*
[2]*Université de Montpellier, Institut des Biomolécules Max Mousseron, CNRS UMR 5247, ENSCM.*

Introduction: Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels that play a central role in neurotransmission in both vertebrates and invertebrates. In insects, they are also the primary molecular targets of several major classes of insecticides, including neonicotinoids and sulfoximines. α1, α8, and β1 subunits assemble to form functional heteromeric receptors when they are expressed in the *Xenopus laevis* oocytes. However, it is unclear whether these different subunits can associate in different stoichiometries. In the present study, different cRNA ratios were injected into *Xenopus* oocytes, revealing that α1α8β1 heteromeric receptors exist under high and low sensitivity stoichiometries.

Methods: To investigate this, we expressed different ratios of α1, α8, and β1 subunits in *Xenopus laevis* oocytes and characterized the pharmacological properties of the α1α8β1 receptors using the two-electrode voltage-clamp technique and structural modeling approaches.

Results: First, we found that the injection of 1:1:1 ratio led to the expression of functional receptors, which were activated by ACh, and currents were blocked by the nAChRs antagonist, α-bungarotoxin. In addition, the sulfoximine insecticide, sulfoxaflor, appeared as a partial agonist. Injection of α1/α8/β1 10:1:1, 1:1:10 and 10:10:1 cRNA ratios led to the expression of high sensitivity α1α8β1 heteromeric receptors. Conversely, injection of 1:10:1 and 1:10:10 cRNA ratios suggests low sensitivity α1α8β1 stoichiometries. In parallel, structural modeling was performed to predict the most probable receptor assembly. The stoichiometry $(\alpha1)_2\alpha8(\beta1)_2$, with the α1β1α8α1β1 arrangement, emerged as the most likely, providing two α1–β1 interfaces identified as an orthosteric binding site for ACh.

Conclusion: The present study supports the hypothesis that multiple α1α8β1 receptor stoichiometries exist in the honeybee nervous system.

SPECIES-SPECIFIC PROPERTIES OF ASICS IN HUMAN DRG NEURONS

Luca Pigelet[1]; Gwenel Le Prado[2]; Hélène Lubrano Di Scampamorte[3]; Gaëtan Poulen[4]; Nicolas Lonjon[4]; Florence Vachiery-Lahaye[5]; Luc Bauchet[5]; Eric Lingueglia[3]; Emmanuel Bourinet[6]; Emmanuel Deval[3]

[1]*Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), Sophia Antipolis.*
[2]*Institut de Génomique Fonctionnelle (IGF), Montpellier.*
[3]*IPMC, Sophia Antipolis.*
[4]*Department of Neurosurgery, Montpellier CHU.*
[5]*IGF, Department of Neurosurgery, Montpellier CHU.*
[6]*IGF, Montpellier, IPMC, Sophia Antipolis.*

Acid-Sensing Ion Channels (ASICs) are excitatory ion channels activated by extracellular protons. A functional channel is made by the trimeric association of different subunits (ASIC1a, ASIC1, ASIC2a, ASIC2b and ASIC3), leading both to homo- and heterotrimers and a great diversity of channel subtypes. ASICs are widely distributed along the pain neuraxis, including in the peripheral sensory/nociceptive neurons as well as in spinal and supra-spinal pain centers. Interestingly, many ASIC inhibitors tested so far in rodents have analgesic effects, whereas positive modulators are proalgic, highlighting these channels as potential therapeutic targets. Nevertheless, there is now a real need for translational data in humans, and our study show data obtained in human DRG from organ donors, in the context of a scientific research program with the Montpellier hospital and the Agence de la Biomédecine. In particular, we performed a functional characterization of ASICs in dissociated human sensory neurons. Our data show a much ASIC higher expression than in rodents, with some human-specific properties that were further investigated in heterologous expression systems. These findings open new perspectives for ASICs as potential therapeutic targets to treat pain in human.

DO HOMOMERIC ASSEMBLIES OF HUMAN EPITHELIAL SODIUM CHANNELS (ENaC) EXIST? LIMITATIONS OF THE XENOPUS LAEVIS OOCYTES MODEL

Sarah Shoushrah; Simin Sedigh Senokesh; Oliver Rauh ; Mike Althaus
Institute for Functional Gene Analytics, Bonn-Rhein-Sieg University of Applied Sciences, Rheinbach, Germany.

Aim: The epithelial sodium channel (ENaC) is typically a heterotrimeric ion channel composed of αβγ- or δβγ-subunit combinations. However, homomeric ENaCs composed of α- or δ-subunits alone have been suggested to form functional channels which might play a role in Na^+ sensing in immune cells. Here we aim to functionally characterize human homomeric ENaCs in *Xenopus* laevis oocytes.

Methods/Results: *Xenopus* oocytes were injected with cRNA coding for human α- or δ-ENaC alone, or αβγ- or δβγ-ENaC. Transmembrane currents were measured by two-electrode voltage-clamp recordings at -60 mV and ENaC-mediated current-fractions were determined with the ENaC-inhibitor amiloride. Oocytes expressing homomeric α- or δ-ENaC generated >40-fold smaller amiloride-sensitive currents (ΔI_{Ami}) than those expressing heteromeric αβγ- or δβγ-ENaC. When oocytes were injected with increasing concentrations of cRNA, unlike heteromeric-ENaCs, the magnitude of ΔI_{Ami} of homomeric ENaCs did not increase with the concentration of cRNA, suggesting a rate-limiting endogenous factor. qPCR experiments revealed the expression of endogenous *Xenopus* β- and γ-ENaC subunits in oocytes, suggesting

they might form heteromeric assemblies with the human α- or δ-subunits. Overexpression of chimeric-ENaCs composed of human (*h*) α- or δ-ENaC and *Xenopus* (*x*) β- and γ-ENaC (*h*α_*x*βγ-ENaC or *h*δ_*x*βγ-ENaC) yielded large ΔI_{Ami}, demonstrating they can form functional ion channels. The IC_{50} values, voltage-dependency, *and* electric-distance for amiloride-inhibition were indistinct between overexpressed chimeric and homomeric ENaCs. Furthermore, homomeric and overexpressed chimeric ENaCs were indistinguishable using two independent experimental strategies: (1) Human and *Xenopus* αβγ-ENaCs are activated by the protease chymotrypsin which cleaves the channel's γ-subunit. Consistently, chymotrypsin activated heteromeric ENaCs but had no effect on homomeric ENaCs. However, chimeric *h*α_*x*βγ-ENaC or *h*δ_*x*βγ-ENaC were also unaffected by chymotrypsin, despite presence of a *x*γ-subunit. (2) The ENaC-activator S3969 specifically interacts with the channel's β-subunit. Despite absence of a (heterologously expressed) β-subunit, currents generated by homomeric human ENaCs were increased by S3969, to the same magnitude as chimeric *h*α_*x*βγ-ENaC or *h*δ_*x*βγ-ENaC.

Conclusion: In *Xenopus* oocytes, currents generated by the expression of human homomeric ENaCs are likely due to heteromeric chimeric ENaCs containing endogenous *Xenopus* ENaC subunits. *Xenopus* oocytes are therefore not a suitable model to study putative single-subunit ENaC assemblies.

RESHAPING THE BINDING POCKET OF APC SUPERFAMILY SOLUTE CARRIERS (SLCS)

George Parsons[1]; Noel Edwards[1]; Catriona Anderson[2]; David Thwaites[1]
[1]*Biosciences Institute, Newcastle University, UK.*
[2]*School of Natural and Environmental Sciences, Newcastle University, UK.*

The Amino Acid-Polyamine-organoCation (APC) Superfamily comprises a huge diversity of transporters including those for ions, metals, osmolytes, vitamins, sugars, neurotransmitters and amino acids. The vast majority of these APC transporters consist of the same core scaffold comprising a 5 + 5 TM inverted structural repeat known as the LeuT fold. In humans, LeuT fold transporters include those in SLC (SoLute Carrier) families 5, 6, 7, 11, 12, 32, 36 and 38. Over the last two decades, a number of crystal structures have been revealed which have shed light on the variations in the binding pocket found in different APC transporter types. However, it is still not possible to predict substrate selectivity from structural and sequence information alone. Here we characterise the importance of a single residue site within the LeuT fold binding pocket which, when mutated, can dramatically alter the substrate specificity of SLC36, SLC38 and SLC6 amino acid transporters. Systematic replacement of a Phe residue (F159) in TM3 of SLC36A2 (PAT2) with progressively smaller residues (e.g. Ile, Thr, Cys, Gly) leads to gain-of-function whereby progressively larger amino acids can access the binding pocket. Although the SLC36 family consists of only four members in all mammalian species it has undergone a separate and extensive expansion in all insects. Here we utilise naturally-occurring insect SLC36 orthologues that vary greatly in the amino acid occupying the position equivalent to PAT2-F159 and demonstrate that this variation correlates with differing substrate specificity. The binding pocket of any APC transporter is moulded by the size, shape and side-chain charge of multiple positions spread throughout the LeuT fold scaffold,

particularly key positions within TMs 1, 3, 6, 8 and 10. However, our work demonstrates that a single site within an archetypal structural motif can have substantial influence over substrate affinity and selectivity within an important superfamily of diverse membrane transporters.
Supported by The Physiological Society, Newcastle University NUAcT, BBSRC, The Royal Society and the Rank-Prize Fund.

16:00 - **Symposium 2: "Channelopathies & Transporteropathies: rare variants, broad impact"**

Organized by Olga ANDRINI (MeLiS, CNRS UMR 5284, INSERM U1314, Université Lyon 1 Claude Bernard, France)

GABA HOMEOSTASIS AND NEURODEVELOPMENT: HOW SLC6A1 (GAT1) MUTATIONS DISRUPT GABAERGIC TRANSMISSION

Elena Bossi; Tiziana Romanazzi; Chiara D'Agostino; Giulia Casoli
Laboratory of Cellular and Molecular Physiology (LFCM) Department of Biotechnology and Life Sciences (DBSV), Centre for Neuroscience Università dell'Insubria.

GABAergic signaling plays a fundamental role in regulating neuronal excitability and neurodevelopment. The GABA transporter 1 (GAT1), encoded by SLC6A1, is a key determinant of synaptic GABA homeostasis. Mutations in SLC6A1 have been increasingly associated with rare neurodevelopmental disorders, including epilepsy, developmental delay, and autism spectrum disorders. However, the mechanistic impact of these variants on transporter function remains incompletely understood. We performed a biophysical and pharmacological characterization of six recurrent SLC6A1 variants identified in patients. Using electrophysiological recordings and by heterologous expression in Xenopus laevis oocytes, we measured transporter-associated currents and determined I_{max} and apparent $K_{0.5}$ values for each functional mutant to assess changes in substrate affinity and transport efficiency. In parallel, we evaluated drug interaction profiles of these variants to define possible therapy. Our results reveal distinct functional impairments across variants. Notably, several variants exhibit a marked decrease in transport-associated currents and important changes in substrate affinity, consistent with impaired GABA uptake capacity, while others show shifts in current parameters that may significantly impact synaptic GABA dynamics. Our findings provide functional insight into how SLC6A1 mutations disrupt GABA homeostasis in different ways, contributing to neurodevelopmental dysfunction. By linking specific biophysical and pharmacological alterations to disease-associated variants phenotype, this work advances our understanding of GAT1 dysfunction and may inform the development of targeted therapeutic strategies.

MOLECULAR PATHOLOGY OF CYSTIC FIBROSIS ASSOCIATED RARE CFTR MUTATIONS

László Csanády; Olivér Závoti; Márton Simon
Semmelweis University.

Mutations of the epithelial anion channel Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cause cystic fibrosis (CF), a rare inherited devastating multiorgan disease. The CFTR channel is gated by ATP binding and hydrolysis at its two cytosolic nucleotide binding domains (NBDs), and regulated through phosphorylation of its unique cytosolic regulatory (R) domain by protein kinase A (PKA). The more than 400 CFTR mutations confirmed to be associated with CF may impair polypeptide synthesis (Class I), protein folding and maturation (Class II), channel gating and regulation (Class III), or anion permeation through the open pore (Class IV). Recent development of highly efficient CFTR modulator drugs, "correctors" that promote folding and "potentiators" that promote gating of mutant CFTR channels, have brought unprecedented symptomatic improvement to CF patients carrying a subset of these mutations. Molecular characterization of all rare variants and their responsiveness to clinically employed modulator drugs is therefore a timely endeavour. We have recently investigated the molecular pathologies and pharmacological profiles of several rare CFTR variants that fall into Classes II, III, and IV. The talk will summarize methodologies used for mutation classification, functional consequences of all the investigated mutations, as well as recommendations for pharmacological treatment.

DOMINANT EFFECTS OF LOSS- AND GAIN-OF-FUNCTION VARIANTS IN NEURONAL ENDOSOMAL CLC TRANSPORTERS

Michael Pusch; Eugenia Rubino; Abraham Tettey-Matey; Alice Giusto; Francesca Sbrana; Maria Antonietta Coppola; Cristiana Picco; Paola Gavazzo; Margherita Festa; Raffaella Barbieri

Istituto di Biofisica, CNR, Genova, Italy.

Genetic variants in autosomal CLCN3 and X-linked CLCN4, which encode the neuronal endosomal Cl^-/H^+ antiporters ClC-3 and ClC-4, are associated with neurodevelopmental disorders characterized by broad phenotypic variability. To date, more than sixty CLCN4 variants and fewer than ten CLCN3 variants have been functionally characterized, revealing both gain- and loss-of-function (GoF and LoF) effects. While ClC-3 can operate as a homodimer, ClC-4 relies on heterodimerization with ClC-3 for efficient endosomal trafficking. Recently, the single-pass membrane proteins TMEM9 and TMEM9B have been identified as essential β-subunits of ClC-3 and ClC-4, exerting an inhibitory effect on CLC transport activity.

In vitro expression studies, combined with electrophysiology and fluorescence microscopy, have uncovered diverse functional consequences of CLCN3 and CLCN4 disease-associated variants. These include toxic GoF effects on ion transport, dominant-negative effects in heterodimeric ClC-3/ClC-4 complexes due to shifts in the voltage dependence of transporter activation, and toxic GoF effects resulting from reduced inhibitory modulation by TMEM9/TMEM9B.

These findings are directly relevant for affected patients and their families, as they facilitate the assessment of the pathogenicity of variants of uncertain significance. Moreover, they provide mechanistic insight into the regulation of ClC-3- and ClC-4-mediated transport by membrane voltage and accessory proteins. Finally, the methodologies established here offer

a valuable framework for future investigations of CLCN3 and CLCN4 variants, particularly those exhibiting novel functional phenotypes in the context of heteromeric ClC-3/ClC-4 complexes.

IN VIVO CHARACTERIZATION OF A DISEASE-ASSOCIATED NALCN VARIANT USING A CONDITIONAL KNOCK-IN MOUSE MODEL

Alexandra Typou[1]; Tanya Phamban[1]; Nattaya Thongsepee[1,2]; Lidiane Pereira-Garcia[1]; Xavier Bonnefont[1]; Hélène Hirbec[1]; Arnaud Monteil[1,3]

[1]*Institute of Functional Genomics, University of Montpellier, CNRS, Inserm, France.*
[2]*Department of Preclinical Science, Faculty of Medicine, Thammasat University, Thailand.*
[3]*Department of Physiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.*

NALCN (sodium leak channel, non-selective) mediates background sodium conductance in neurons and other excitable cells, helping maintain a depolarized resting membrane potential. Both inherited loss-of-function and *de novo* gain-of-function mutations in *NALCN* cause ultra-rare neurodevelopmental disorders with onset in early infancy. Affected individuals present with a broad clinical spectrum, including global developmental delay, apnea, hyperkinetic movement disorders, and increased childhood mortality.
Here, we generated a Cre-dependent knock-in mouse model carrying a *de novo NALCN* variant identified in at least six unrelated patients. To drive neuronal expression throughout the central nervous system, the line was crossed with Nestin-Cre mice. Mutants showed high lethality (75%), and survivors exhibited hyperlocomotion, anxiety-like behavior, disrupted circadian rhythms, and reduced motivation. They also displayed early developmental delay, microcephaly, ventriculomegaly and cortical aplasia.

Electrophysiological recordings from hippocampal neurons revealed altered passive membrane properties, indicating a direct effect of the variant on neuronal function. This model recapitulates key clinical and neurobiological features of *NALCN*-related disorders and provides the first *in vivo* evidence of the developmental impact of this variant. Overall, it offers a robust and clinically relevant platform to investigate disease mechanisms and support the development of targeted therapies.

17:45 - **Oral communication session 2: "Ion channels in cancer: from cellular adaptation to therapeutic response"**

Organized by Valerio FARFARIELLO (CRCLille, INSERM U1366, Université de Lille, France)

EXPRESSION PROFILING OF TRPM2 IN COLORECTAL CANCER: A COMBINED IN SILICO AND EX VIVO ANALYSIS.

Juan Manuel Gómez-Sedeño[1]; Niza Ureña-Rodríguez[2]; José María Remes-Troche[1]; Arturo Meixuero-Daza[3]; Peter Grube-Pagola[3]; Job Reyes-Huerta[3]; Cynthia Daniela Ibarra-Moreno[4]; Eloy Andrés Pérez-Yépez[5]; Adriana Sumoza-Toledo[1]

[1]*Master in Translational Biomedicine. Institute of Medical-Biological Research, Universidad Veracruzana. Agustín de Iturbide S/N. Col. Flores Magón.Veracruz, Ver., México. CP.91700.*

[2]*Master in Clinical Chemistry, Faculty of Bioanalysis, Universidad Veracruzana. Agustín de Iturbide S/N. Col. Flores Magón. Veracruz, Ver., México. CP.91700.*
[3]*Institute of Medical-Biological Research, Universidad Veracruzana. Agustín de Iturbide S/N. Col. Flores Magón.Veracruz, Ver., México. CP.91700.*
[4]*Instituto Tecnológico y de Estudios Superiores de Monterrey, Escuela de Medicina y Ciencias de la Salud. Mexico city, Mexico.*
[5]*Laboratorio de Señalización celular e Inmunología del cáncer (SECIC), Instituto Nacional de Cancerología, San Fernando 22. Col. Sección XVI, Tlalpan, Mexico city, Mexico. CP. 14080.*

TRPM2 is a non-selective cation channel primarily permeable to Ca^{2+} that regulates cellular processes associated with oxidative stress, inflammation, and cell survival. Aberrant TRPM2 expression has been reported in numerous pathological conditions, including cancer; however, its expression profile in colorectal cancer (CRC) remains incompletely characterized. This study aimed to evaluate TRPM2 expression in CRC by integrating *in silico* bioinformatic analyses with ex vivo immunofluorescence of human tumor tissues. TRPM2 gene expression in normal and tumor tissues from colon adenocarcinoma (COAD) and rectal adenocarcinoma (READ) was analyzed using the publicly available TNMplot and UALCAN platforms, with additional evaluation according to clinicopathological characteristics, including tumor stage. TIMER3 was also used to investigate the relationship between TRPM2 expression and immune cell infiltration. Lastly, TRPM2 protein expression was assessed by immunofluorescence in CRC tissue specimens obtained from patients. The *in silico* analyses revealed significant TRPM2 overexpression in both COAD and READ compared with normal tissues ($p<0.001$). Tumor stage analysis showed significant differences between tumor and normal tissues, with no significant differences among tumor stages, suggesting that TRPM2 upregulation is an early and sustained event during CRC progression. Furthermore, TRPM2 expression showed weak but significant positive correlations with macrophage and CD8+ T-lymphocyte infiltration estimated by TIMER3. Immunofluorescence analysis confirmed TRPM2 protein expression in human CRC tissues. Collectively, these findings suggest that TRPM2 is consistently overexpressed in CRC, independently of tumor stage, and support its potential value as a candidate diagnostic biomarker for CRC. Additional mechanistic and clinical studies are needed to define its functional and prognostic significance.

MEMBRANE DEPOLARIZATION DRIVES WNT/β-CATENIN SIGNALING IN COLONIC HOMEOSTASIS AND COLORECTAL CANCER

Estefania Torres Ortiz
Institute of Biology Valrose

Membrane potential has historically been studied for its role in molecular signaling and cell fate decisions in neuronal and developmental contexts. However, its contribution to signaling pathways across adult epithelia remains poorly understood. The colon provides an ideal system of study due to its continuous epithelial turnover, where disrupted homeostasis drives colorectal cancer progression. Here, we uncovered an endogenous bioelectrical crypt-lumen pattern characterized by depolarized proliferating crypt cells and hyperpolarized differentiated luminal cells. This pattern aligns with the well-known WNT and BMP counter-gradient that governs stem cell maintenance and differentiation, respectively, along the

colonic crypt. This spatial organization suggests that membrane potential variations may act as a molecular switch controlling chemical signals. To address this question, our research relies on a blue light optogenetic system that depolarizes the membrane by activating channelrhodopsin-2 expressed in transfected HT29 cells and mouse colon 3D organoids. Membrane depolarization directly activated the canonical Wnt/β-catenin pathway, as shown by increased β-catenin/TCF-dependent transcriptional activity measured using the 7xTcf-eGFP reporter. To assess Wnt-dependent regulation of bioelectrical gradient, we first inhibited wnt ligand secretion, which interestingly abolished the observed spatial bioelectrical pattern. Ultimately, depolarization increased organoid diameter, suggesting that bioelectric modulation drives morphological changes linked to Wnt/β-catenin signaling and tissue growth regulation. Together, these findings establish a novel feedback loop between membrane potential and signaling pathways critical for colonic epithelial homeostasis.

CARBOXYAMIDOTRIAZOLE IMPACTS STORE-OPERATED CALCIUM ENTRIES AND DECREASES STEM-LIKE PROPERTIES IN GLIOBLASTOMA STEM CELLS

Théo Branchu; Laëtitia Cousin; Thomas Harnois; Tom Materna; Bruno Constantin; Nadine Déliot; Valérie Coronas
Laboratory Channels and Connexins in Cancer and Cell Stemness, University of Poitiers, France.

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. Despite standard treatment combining surgery, radiotherapy, and temozolomide (TMZ), prognosis remains poor due to frequent recurrence driven by glioblastoma stem cells (GSC). These cells exhibit self-renewal, therapeutic resistance, and high adaptability to the tumor microenvironment. Calcium signaling, particularly store-operated calcium entry (SOCE) mediated by STIM1 and Orai1, plays a key role in GSC maintenance and represents a promising therapeutic target as it can be dysregulated in several cancer types. Interestingly, a phase Ib clinical trial showed that carboxyamidotriazole (CAI), an inhibitor of non-voltage-gated calcium channels, combined with TMZ improved survival in GBM patients and was well tolerated. This study investigated the effects of CAI and/or TMZ on calcium signaling in patient-derived mesenchymal (GBM1) and non-mesenchymal (GBM5) GSC. CAI alone efficiently and dose-dependently inhibited SOCE in both cell lines. The absence of an additional effect with GSK-7975A suggests that Orai channels are one of its targets. Functionally, CAI significantly reduced GSC proliferation, self-renewal, and migration with GBM5 cells being more sensitive to CAI than GBM1 cells. Combined with TMZ, CAI maintained its inhibitory effect on SOCE, whereas TMZ alone had no major impact. Co-treatment reduced cell viability and clonogenic capacity more effectively than either treatment alone. Notably, CAI prevented TMZ-induced senescence in GBM1 cells, a state associated with therapeutic resistance and tumor recurrence, suggesting that CAI may limit the emergence of resistant GSC populations. Overall, these findings highlight the essential role of calcium signaling, and particularly SOCE in GSC maintenance and identify CAI as a promising strategy to enhance TMZ efficacy and overcome treatment resistance in GBM.

TRPM2 PROMOTES THERAPEUTIC RESISTANCE IN TRIPLE-NEGATIVE BREAST CANCER THROUGH THE REGULATION OF INTRACELLULAR CALCIUM HOMEOSTASIS

Alice Hasselsweiller[1]; Mayar Soussi[1]; Dmitri Gordienko[1]; Ayşenur Nazıroğlu[2]; Mustafa Nazıroğlu[3]; Loïc Lemonnier[1]; Evan Courmont[1]; Anna Rita Cantelmo[4]; Chann Lagadec[1]; Dimitra Gkika[1]

[1]Univ. Lille, Inserm, CHU Lille, CNRS, U1366-UMR9020 – CRCLille – Cancer Research Center of Lille, F-59000 Lille, France.

[2]Department of Histology and Embryology, Health Science Institute, Suleyman Demirel University, Isparta, Türkiye.

[3]Department of Biophysics, Medical Faculty, Suleyman Demirel University, Isparta, Türkiye.

[4]U1011-EGID, F-59000 Lille, France.

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype characterized by the absence of hormone receptors and HER2 overexpression, limiting targeted treatment options and contributing to a high risk of relapse. In this context, identifying novel mechanisms involved in treatment resistance remains a major challenge.

Transient Receptor Potential (TRP) channels, particularly TRPM2 (Transient Receptor Potential Melastatin 2), have been identified as dysregulated in TNBC cells exposed to chemotherapy. Survival analyses revealed that high TRPM2 expression is associated with poor prognosis in treated TNBC patients. These clinical findings were supported by experimental data showing increased TRPM2 expression in TNBC cell lines following chemotherapy exposure. This upregulation, observed at both the transcriptional and protein levels, suggests enhanced TRPM2 activity in response to treatment-induced stress.

Functional studies demonstrated that TRPM2 activation, either by cumene hydroperoxide (Cpx), a TRPM2 agonist, or by hydrogen peroxide (H_2O_2), increases tumor cell viability, whereas TRPM2 inhibition promotes cell death. In addition, immunofluorescence analyses revealed a predominantly intracellular localization of TRPM2. Our results further indicate that TRPM2 is involved in the regulation of mitochondrial calcium homeostasis, suggesting a key role in cellular survival mechanisms and adaptation to therapy-induced stress.

Taken together, these findings support the hypothesis that TRPM2 actively contributes to therapeutic resistance in TNBC. Targeting this channel may therefore represent a promising strategy to restore tumor cell sensitivity to conventional treatments. Further investigations using preclinical models and patient tumor samples will help to better define the therapeutic potential of TRPM2 and evaluate its relevance as a predictive biomarker of treatment response.

Tuesday, September 8th, 2026

08:45 - **Symposium 3: "The neglected CRAC Proteins : Orai2, Orai3 and STIM2"**

Organized by Bruno CONSTANTIN (IFR Santé, Laboratoire 4CS, Université de Poitiers, CNRS UAR BioS N° 2038)

STIM2 AND ORAI AND CALCIUM ENTRIES

Barbara Niemeyer

Molecular Biophysics. Saarland University, Saarbrücken, Germany.

Communication between cells and organs relies on the release of signaling molecules or on direct interaction between cells. Release of cytokines and vesicular release is commonly triggered by a rise in intracellular Ca^{2+} and alterations of these Ca^{2+} signatures often underlie pathogenic signaling. Many neuromodulators and several hormones directly recruit and activate ER-resident stromal interaction molecules (STIM), which activate Orai ion channels to allow store-operated Ca^{2+} entry (SOCE). While it is known that SOCE is essential for the release of cytokines or cytotoxic vesicles in immune cells, its direct and/or indirect role in transmitter release and secretory mechanisms in non-immune cells, however, is insufficiently understood. *STIM* genes contain multiple predicted splice variants with cell type specific functions that are just beginning to be understood and may underlie the divergent phenotypes of STIM1 GOF or LOF mutations. On the other hand, the ion channel composition of ORAI ion channels subunits also determines the activity and regulatory aspects of I_{CRAC}. The differential roles of STIM and ORAI proteins in regulation and function of both immune and non-immune cells will be discussed.

FUNCTIONAL ROLE OF ORAI3 IN THE PATHOPHYSIOLOGY OF LUMINAL BREAST CANCER

Juan A. Rosado

University of Extremadura, Badajoz,Spain.

The Orai family of proteins constitutes the pore-forming subunits of channels mediating store-operated Ca^{2+} entry (SOCE). In luminal, estrogen receptor positive (ER+), breast cancer cells, the Orai1-Orai3 landscape undergoes a unique remodeling. While Orai1 is typically the primary SOCE component in most tissues, in ER+ breast cancer, SOCE is predominantly dependent on Orai3, whereas Orai1 serves as a critical upstream regulator of Orai3 expression and alternative Ca^{2+} influx pathways. Recent studies demonstrate that Orai1 is functionally essential for sustaining Orai3 synthesis and protein stability. In Orai1-knockout (O1KO) ER+ breast cancer cells, Orai3 expression is significantly attenuated due to enhanced endo-lysosomal degradation and reduced synthesis. This regulation is mediated through an ERα-Orai3 axis, where Orai1 maintains ERα levels and modulates NFAT2 nuclear translocation. Consequently, loss of Orai1 indirectly impairs SOCE by depleting Orai3 protein levels.

Beyond expression, Orai1 and Orai3 exert opposing functional effects on the PI3K/Akt1 signaling pathway, a key determinant of tumor aggressiveness. Using O1KO cells, siRNAs, and

pharmacological inhibitors, our recent results indicate that Orai3 promotes Akt1 activation via a Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) pathway. Both Orai3 overexpression and 2-APB-mediated stimulation enhanced Akt1 phosphorylation. Conversely, Orai1 acts as a negative modulator of this axis. Orai1 deficiency or knockdown resulted in enhanced Akt1 phosphorylation, an effect mimicked by increasing cAMP levels and impaired by silencing the Ca^{2+}-sensitive adenylyl cyclase 8 (AC8). Notably, the Orai1-mediated inhibition of Akt1 requires Ca^{2+} influx, as the pore-dead Orai1-E106Q mutant failed to affect phosphorylation. In conclusion, our findings reveal a complex regulatory network where Orai1 governs the stability of the ERα-Orai3 axis while simultaneously dampening Akt1 activation through an AC8/cAMP-dependent mechanism. Meanwhile, Orai3 directly drives Akt1-mediated aggressiveness. These results highlight the functional diversity of Orai proteins and identify the Orai1-Orai3 interplay as a sophisticated therapeutic target for modulating signaling in ER+ breast cancer.

DEMYSTIFYING THE MYSTERY OF ORAI3 FUNCTION AND REGULATION IN PANCREATIC CANCER

Rajender Motiani

Laboratory of Calciomics and Systemic Pathophysiology (LCSP), UNESCO-Regional Centre for Biotechnology (RCB), Delhi-NCR, Faridabad, India.

Pancreatic cancer is one of the deadliest cancers, and there is a critical need to better understand the mechanisms that drive its progression and therapy resistance. In our recent work, we identified Orai3, a calcium channel, as a novel regulator of pancreatic cancer metastasis and chemoresistance. By analyzing public datasets, we found that Orai3 is overexpressed in patient samples, and that higher Orai3 levels are associated with poorer clinical outcomes. However, how Orai3 expression is regulated has remained largely unappreciated. In this talk, I will share our recent findings revealing a surprising, dual role for the transcription factor NFATc1 in both promoting Orai3 transcription and driving its lysosomal degradation. Finally, I will discuss the potential clinical relevance of this context-dependent signaling pathway.

STIM2 MUTATIONS FOUND IN A PATIENT WITH NON-TUBERCULOUS MYCOBACTERIUM INFECTION DISPLAY ALTERED STORE-OPERATED Ca^{2+} INFLUX (SOCE)

Leonie Hoppe[1]; Stefan Feske[2]; Aseervatham Anusha Amali[3]; Louis Chai[3]; Barbara A. Niemeyer[1]

[1]*Molecular Biophysics, Saarland University, Homburg, Germany.*

[2]*Department of Pathology, New York University (NYU), New York, USA.*

[3]*Department of Medicine, National University Hospital, Singapore.*

Abnormal store-operated Ca^{2+} entry (SOCE) can result in altered immunity and susceptibility to infections. This has to date been described in patients bearing mutations in STIM1 and ORAI1. In a patient with *Mycobacterium avium* pulmonary infection, whole exome sequencing

revealed two mutations within the C-terminal region of the STIM2 gene. To address whether cells mimicking the complex heterozygous genotype of the patient alter Ca^{2+} signaling, we used STIM2 deficient SHSY-5Y cells to re-express prior mutagenized constructs harboring either single or both mutations and possessing differential fluorescent tags in their respective N-terminal domains. The cells were then subjected to a complex Ca^{2+} imaging protocol using Fura-2 as a ratiometric dye to assess differences in basal cytosolic Ca^{2+} levels and in induced Ca^{2+} entry after depolarization or after triggering store-operated Ca^{2+} influx (SOCE). We also analyzed potential effects of the patient derived mutations within the inhibitory splice variant of STIM2 (STIM2.1).

17:15 - **Symposium 4: "Intracellular ion channels in health and diseases"**

Organized by Natacha PREVARSKAYA (CRCLille laboratory, UMR9020 CNRS - U1366 Inserm - Université de Lille - CHU de Lille - Université de Picardie Jules Verne Team IoniC)

STRUCTURAL INSIGHTS INTO ISOFORM-SPECIFIC REGULATION OF IP3 RECEPTORS.

Irina I. Serysheva

Department of Biochemistry and Molecular Biology, McGovern Medical School, University of Texas Health Science Center, Houston, Texas 77030, USA, MD Anderson Cancer Center, UTHealth Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA.

Calcium release through inositol 1,4,5-trisphosphate receptors (IP3Rs) is a central mechanism for intracellular signaling that regulates muscle contraction, neuronal activity, and diverse physiological processes. Despite sharing a conserved tetrameric architecture, the three mammalian IP3R isoforms (IP3R1–3) exhibit distinct regulatory properties and physiological roles that have remained incompletely understood at the structural level. Recently, we solved near-atomic cryo-EM structures of full-length IP3R2 in both ligand-free and Ca^{2+}/IP3/ATP-bound states, enabling comparative structural analyses across IP3R isoforms and defining the architectural basis of subtype-specific regulation and channel activation. IP3R structures reveal a unified gating mechanism in which ligand binding at the IP3-binding cleft is allosterically coupled to pore opening through long-range domain rearrangements. Although the IP3-binding pocket is conserved across isoforms, differences in ligand sensitivity arise primarily from isoform-dependent conformational dynamics of the ARM2 regulatory domain rather than changes in binding-site residues.

We propose that the ARM2 loop functions as a "dynamic gate" that controls access to the ligand-binding cleft. Unlike a static steric barrier, ARM2 undergoes isoform-tuned conformational fluctuations that may regulate transitions between accessible and restricted states through coordinated extended-retracted motions. In the extended configuration, ARM2 likely maintains partial cleft accessibility while permitting the conformational flexibility within the binding pocket required for ligand accommodation. Conversely, the retracted state promotes tighter interdomain packing, stabilizing ligand engagement. Isoform-specific differences within the ARM2 shift this conformational equilibrium between these states, providing a mechanistic basis for differential IP3 sensitivity across IP3R subtypes.

We further define a conserved ATP-binding site that modulates activation by stabilizing interdomain coupling at the cytosol–membrane interface, thereby enhancing transmission of ligand-induced conformational changes to the transmembrane pore. At the pore, activation converges on the TM6 bundle crossing, where ion conduction is governed not by large-scale dilation but by dynamic side-chain rearrangements at hydrophobic constriction sites, enabling transient Ca^{2+} permeation.

Together, these findings establish a structural framework for IP3R gating across isoforms, in which conserved architecture is differentially regulated through domain dynamics, allosteric coupling, and isoform-specific modulatory elements, thereby explaining how IP3R1–3 generate distinct cellular Ca^{2+} signaling outputs.

NAADP EVOKED CALCIUM SIGNALING

Andreas H. Guse

Center for experimental medicine, The Calcium Signaling Group, Department of Biochemistry and Molecular Cell Biology, University Medical Center Hamburg-Eppendorf, Germany.

Nicotinic acid adenine dinucleotide phosphate (NAADP) is a Ca^{2+} mobilizing 2nd messenger involved in autoimmunity of the CNS. Pharmacological antagonism of NAADP signaling in the rat EAE model diminished (i) T cell motility and re-activation upon arrival in the nervous tissues, (ii) the levels of pro-inflammatory cytokines INF-g and IL-17, and (iii) the clinical symptoms of experimental autoimmune encephalomyelitis, indicating that NAADP signaling pathway is essential for the recruitment and the activation of autoaggressive effector T cells within the CNS[1,2]. More recently, we demonstrated that NAADP initiates ultra-rapid local Ca^{2+} signals in T cells, termed Ca^{2+} microdomains[3,4]. We discovered essential components of NAADP signaling, e.g. a redox cycle involving dual NADPH oxidase 2 (DUOX2) as NAADP-forming enzyme[5] , HN1L/JPT2 as NAADP receptor[6], and the type 1 ryanodine receptor (RYR1) as Ca^{2+} release channel targeted by NAADP/HN1L/JPT2[3,4]. Ca^{2+} microdomains are initiated by NAADP that activates RYR1 via HN1L/JPT2[3,4]. In addition, they are rapidly amplified by store-operated Ca^{2+} entry via Orai1[4] and via P2X4 and P2X7 purinergic receptors/channels[7].

For direct activation of NAADP signaling in intact cells, we developed MASTER-NAADP, a membrane-permeant precursor that releases a NAADP mimetic[8].

Very recently, we identified multiple pathways that activate the NAADP forming activity of DUOX2 in T cells[6], involving cAMP signaling via PKA Cb2 and PKCQ[9].

The relevance of the NAADP/Ca^{2+} signaling pathway for inflammation will be discussed for the EAE model of multiple sclerosis.

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ENDOLYSOSOMAL TRPMLs/TPCs: NEW ASPECTS OF THEIR PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL RELEVANCE

Christian Michael Grimm

Department of Pharmacology, University of Oxford, Department of Pharmacology, LMU University of Munich, Fraunhofer Institute Munich.

Research on endolysosomal ion channels and transporters has gained considerable momentum in recent years, as new technologies are now available to investigate the function, physiology, and pathophysiology of these important intracellular membrane proteins in more detail. For example, endolysosomal patch-clamp electrophysiological techniques, intracellular sensors for endolysosomal Ca2+ and pH measurements or new animal models have been developed. Using these techniques, it has been discovered that endolysosomal cation channels such as TRPML channels or two-pore channels (TPCs) play important roles in a variety of organs and that defects or alterations in their function are associated with lysosomal storage diseases and neurodegenerative diseases, infectious diseases, immune cell dysfunction, lung, liver and heart diseases as well as cancer (e.g., melanoma). Thanks to significant advances also in the availability of pharmacological tools for these novel endolysosomal membrane proteins, accompanied by numerous cryo-EM structures, research in this area is progressing rapidly. We aim to present recent and current findings on functional, physiological and pathophysiological roles of TRPML channels and TPCs.

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BIOPHYSICAL PROPERTIES OF ACID-SENSITIVE TWIK1 DYNAMIC SELECTIVITY: INSIGHTS INTO IRON METABOLISM

Quentin Lelievre[1]; Isabelle Rubera[1]; Christophe Duranton[1]; Jacques Barhanin[1]; Fatima Nachit[1]; Franck Chatelain[2]; Florian Lesage[2]; Saïd Bandahhou[1]

[1]LP2M.

[2] IPMC.

TWIK1 is a two-pore domain potassium (K2P) channel predominantly localized in recycling endosomes, where luminal acidification triggers a unique conformational transition that switches the channel from a K^+-selective to a Na^+-permeable state. Although the structural

basis of this dynamic ion selectivity has been established, whether this transition regulates channel activity and contributes to endosomal physiology remains unknown. Here, we investigated how acidification-dependent conformational changes control TWIK1 function from the single-channel to the cellular level.

Single-channel activity was analyzed in cell-attached patches using trafficking-competent TWIK1 constructs carrying mutations that either favor or impair the conformational transition. Wild-type TWIK1 and the gain-of-function mutant K274E were further characterized in planar lipid bilayers, and whole-cell recordings were used to relate unitary behavior to macroscopic currents. Wild-type TWIK1 displayed a very low basal open probability (Po ≈ 0.04), indicating that its limited activity mainly reflects infrequent channel opening. Strikingly, channels adopting the Na^+-permeable conformation consistently exhibited a significantly higher open probability than those remaining in the K^+-selective state, revealing that the conformational transition induced by acidification enhances channel gating. This effect fully accounted for the gain-of-function phenotype of K274E and was also seen in whole-cell currents.

Because endosomal acidification is essential for transferrin receptor-mediated iron uptake, and TWIK1 knockout mice exhibit a phenotype consistent with altered iron homeostasis, we next investigated the physiological relevance of this mechanism in renal proximal tubule cells, where both TWIK1 and transferrin receptor 1 (TfR1) are highly expressed. While TWIK1 deletion did not affect membrane polarization or direct Fe^{2+} uptake, it significantly impaired transferrin-dependent iron internalization, identifying TWIK1 as a novel regulator of endosomal iron uptake.

Together, our findings demonstrate that endosomal acidification not only alters the ion selectivity of TWIK1 but also enhances its activity through a functional coupling between permeation and gating. This mechanism reveals how dynamic ion selectivity can act as a regulatory switch to control intracellular ion channel function and endosomal physiology.

Wednesday, September 9th, 2026

09:30 – Symposium 5: "Adaptation: how ion channels enable cells to detect changes"

Organized by Joël Tabak (University of Exeter, England)

ADAPTIVE ACTION POTENTIALS AND SPIKE CODING IN C. elegans

Qiang LIU

Liu lab, City University of Hong Kong, Hong Kong.

For decades, C. elegans neurons were thought to operate purely through analog signaling, with no action potentials and no spike-based coding. Our recent work overturns this view. We identified three spiking neuron types in worms and characterized their digital coding schemes, revealing that the C. elegans nervous system uses hybrid analog-digital computation to drive a range of behaviors. To connect the connectome to a working whole-brain model, we are systematically collecting whole-cell electrophysiological recordings from all 106 somatic neuron types, building what we call a comprehensive "electrophysiome" of the entire nervous system. Preliminary data from roughly half of these neurons already reveal striking biophysical diversity and distinct computational specializations across cell types, demonstrating that this goal is well within reach. The next step is constructing conductance-based single-neuron models and integrating them with the existing connectome in a bottom-up whole-brain model.

Beyond the nervous system, we made an unexpected discovery: action potential spikes in C. elegans intestinal epithelial cells, with waveform properties reminiscent of mammalian cardiac action potentials. Prior work established that IP3R-mediated intestinal calcium waves drive the rhythmic defecation motor program (DMP) in C. elegans, but these new results raise the possibility that membrane potential oscillations interact with calcium release from internal stores to generate the enteric rhythm. We are currently working to identify the possible pacemaker in the intestine, define the ionic mechanisms underlying intestinal spiking, and characterize the relationship between calcium dynamics and membrane potential through simultaneous calcium/voltage imaging and quantitative modeling.

HOW THE AUDITORY SYSTEM ACHIEVES HIGH DYNAMIC RANGE

Lina Maria JAIME TOBON

Institute for Neurosciences of Montpellier, Montpellier, France.

Our ability to hear relies on encoding a broad range of sound pressures spanning over six orders of magnitude while maintaining exquisite temporal resolution. This remarkable capacity is believed to stem from the auditory system's neural diversity. Specifically, cochlear sensory cells exhibit anatomical and functional synaptic diversity along their basolateral surfaces, including variations in calcium channel properties. This talk will highlight how this

heterogeneity enables the decomposition of sound information and contributes to a population code that captures the complexity of the sound environment.

IONIC MECHANISMS OF PARASYMPATHETIC REGULATION OF HEART RATE

Marvin GAILLARDON[1]; Mélanie Faure[1]; Isabelle Bidaud[1]; Anne Vincent-Fagot[1]; Steven Marx[2]; Pietro Mesirca[1]; Matteo Mangoni[1]

[1]Institut de Génomique Fonctionnelle, Montpellier, France.

[2]Columbia Presbyterian Hospital, New York (USA).

Cholinergic regulation of heart rate (HR) is mediated by acetylcholine (ACh)-dependent activation of M2-receptors (M2R). Activated M2R promote release of the βγ-subunit of G-proteins to directly gate GIRK1/4 channels (underlying I_{KACh}),αi-subunits inhibit adenylate cyclase (AC) activity. AC inhibition reduces the intracellular concentration of cAMP, decreasing the activity of ion channels involved in pacemaking, including HCN4 and L-type calcium channels. We showed that RAD-dependent regulation of L-type Cav1.3 and cAMP-dependent regulation of HCN4 channels are important in β-adrenergic activation of HR in mice. Here, we aim to determine the importance of those channels in cholinergic regulation of HR .
We recorded the HR of isolated Langendorff perfused hearts in wild-type, GIRK4 knockout (GIRK4KO, no I_{KACh}), HCN4-CNBDa (no cAMP-dependent regulation of HCN4), 4SA-Rad (no adrenergic regulation of Cav1.3 Ca2+ channels) and GIRK4KO/HCN4-CNBDa double-mutant mice, in control or during ACh perfusion at different doses (10nM, 30nM, 100nM, 300 nM and 1000 nM).

In WT and 4SA Rad isolated hearts, ACh similarly reduced HR in a concentration dependant manner 6.5% vs 5.7% at 10nM Ach; 13.0% vs 13.9% at 30 nM Ach; 18.9% vs 21.5% at 100 nM Ach; 23.3% vs 26.9% at 300 nMAch and 30.1% vs 36.7% at 1000nM Ach). We observed, at baseline conditions, the loss of RAD-dependent regulation of I_{CaL} did not affect cholinergic regulation of HR. HCN4-CNBDa hearts showed lower HR reduction in comparison to control and 4SA-Rad hearts at the highest dose (28%) suggesting a functional role of HCN4 channels in the negative chronotropic regulation of HR in isolated hearts at baseline, even at high ACh doses.

In Girk4 deficient hearts, ACh response was blunted at all the doses tested (in comparison to control condition, reaching a maximum HR reduction value of about 15 % in GIRK4KO and 17% GIKR4/HCN4-CNBDa.

Our data suggest that HCN4 channels play a role in cholinergic regulation of HR at baseline. Concomitant ablation of GIRK1/4 and HCN4 channels abolished regulation in isolated murine hearts. Experiments are ongoing to decipher the role of RAD-dependent regulation of Cav1.3 channels under an accentuated antagonism between adrenergic and cholinergic inputs.

ION CHANNEL-DRIVEN VOLTAGE DYNAMICS AS SPATIAL CUES FOR MORPHOGENESIS IN ASCIDIANS

Josep Martí-Solans; Agnès Roure; Sébastien Darras
Observatoire Océanologique de Banyuls-sur-Mer, CNRS/Sorbonne Université, France.

Ion channels are essential regulators of morphogenesis, yet the mechanistic link between ion channel-driven fluctuations in cell membrane voltage and the coordination of tissue-specific gene expression remains poorly understood. Bridging this gap requires determining how specific ion channel activity provides the physical instructions necessary to shape the developing embryo.

Using the ascidian *Phallusia mammillata* as a model, we are investigating how ion channel activity guides embryonic development. We have integrated high-resolution, live imaging of voltage dynamics, using voltage-sensitive dyes, with spatial expression profiling to map where key ion channel families are active throughout embryogenesis.

Our preliminary mapping reveals that distinct voltage signatures characterize specific embryonic domains, with voltage gradients often appearing before key physical changes. To test the functional necessity of these patterns, we employed targeted pharmacological perturbations. Our data indicate that disrupting specific ion channel activity leads to significant defects in both embryonic axis elongation and the formation of sensory organs. By correlating these electrophysiological signatures with the spatial expression of ion channels and downstream developmental markers, this work aims to establish a mechanistic framework for how ion channel activity integrates with gene regulatory networks to orchestrate complex organogenesis.

POSTER ABSTRACTS

P1 - THE DEUBIQUITINASE UCHL1 REGULATES THE INFLUX OF CATIONS IN NEURONAL CELLS

Marie PERRIER; Marie-Odile FAUVARQUE; Alexandre BOURON
BGE (CEA Grenoble).

Ubiquitination influences a myriad of biological processes including the trafficking and degradation of ubiquitin-tagged target proteins. This post-translational modification can be reversed by deubiquitinating enzymes (DUBs). UCHL1 is a predominant DUB in the brain but its biological functions and substrates remain poorly understood. To further advance our understanding of its cellular functions, we used two selective UCH-L1 inhibitors (IMP1710 or GK13S). This pharmacological approach allowed us to show that UCHL1 inhibition reduces the Ca2+ influx through voltage-gated Ca2+ channels (VGCCs) in cultured embryonic cortical neurons by affecting mainly dihydropyridine-sensitive (L-type) VGCCs. In addition, UCHL1 inhibitors impair intracellular Ca2+ stores and reduce Cav1.2 protein levels in neurons but not in cancer cell lines. We asked whether UCHL1 could regulate the activity of other types of neuronal ion channels. Live-cell fluorescent imaging experiments showed that UCHL1 inhibition reduces ion fluxes through NMDA receptors, TRPC6 and TRPM7 channels. Furthermore, a proteomic analysis was conducted on lysates from embryonic cortical neurons to better characterize the putative UCHL1 targets. Our results showed that UCHL1 inhibition strongly downregulates the DUB USP11. It remains to be determined, however, whether USP11 is acting downstream to UCHL1 and plays a role in the regulation of ion channels. Altogether, this study identifies UCHL1, the main DUB of the brain, as an important regulator of the transport of ions through cell-surface neuronal ion channels and provides further insights into its cellular functions.

P2 - CANCER CELLS INFLUENCE OXALIPLATIN ACTION ON SENSORY NEURON ION CHANNELS AND ACTIVITY

Eléonore Solinas; George Shapovalov; Natacha Prevarskaya
CRC Lille (Centre de Recherche en Cancérologie de Lille).

Pancreatic cancer remains one of the most lethal malignancies, where chemotherapy constitutes the cornerstone of treatment. However, the clinical efficacy of agents like oxaliplatin is severely limited by Chemotherapy-Induced Peripheral Neuropathy (CIPN), leading to debilitating cold-triggered pain and premature treatment termination. While existing literature extensively investigates neurotoxic agents or tumor-secreted factors in isolation, their combined, synergistic impact on sensory pathways remains unaddressed. This work demonstrates that establishing accurate models of CIPN requires the joint consideration of both the oncological microenvironment and chemotherapeutic stress, as their interaction drives a non-linear remodeling of ion channel activity in dorsal root ganglion (DRG) neurons. Using a combination of calcium imaging, patch-clamp recording (current-clamp configuration), and qRT-PCR, we investigated the DRG neurons functional

and transcriptional alterations induced by oxaliplatin, pancreatic cancer cell co-culture, and their combination. We show that this dual challenge induces intracellular calcium dysregulation and alters the expression and biophysical properties of thermosensitive Transient Receptor Potential (TRP) channels. Furthermore, this joint context triggers a distinct remodeling of ion channels responsible for cell excitability and action potential generation. Patch-clamp analysis revealed modifications in action potential kinetics, thresholds, and firing patterns, directly linked to alterations in the underlying voltage-gated ionic currents. These findings underscore that CIPN pathophysiology cannot be decoupled from the cancer context, as both impact DRG ion channels, sometime in an interaction relation.

P3 - CHARACTERIZATION OF THE EXPRESSION OF POLYCYSTIN AND IP3RS CHANNELS IN PANCREATIC DUCTAL ADENOCARCINOMA

Clothilde CONTY[1]; Clémence MERY DE MONTIGNY[1]; Stéphanie GUENIN[2]; François JOBERT[2]; **Lise RODAT-DESPOIX[1]**

[1]Université Picardie Jules Verne, U1366 Inserm, Univ. Lille, CHU Lille, UMR9020 CNRS – CRCLille – Cancer Research Center of Lille Team PancResT « Chemoresistance & Therapeutic Targeting in Pancreatic Cancers ».
[2]Université de Picardie Jules Verne, Centre de Ressources Régionales en Biologie Moléculaire (CRRBM), 80039, Amiens, France.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer characterized by a dense, fibrous stroma and dysregulation of calcium homeostasis. This fibrosis generates mechanical stresses that stimulate the mechanosensitive Piezo calcium channels. However, other mechanotransduction factors deserve consideration in PDAC, such as polycystins (PC1/PC2), whose role in the fibrotic environment of polycystic kidney disease is well established. No data linking PC1 or PC2 to PDAC are available, and PC2's ability to interact with IP_3Rs in the endoplasmic reticulum leads us to propose characterizing their expression and potential co-localization in PDAC.
In this context, the transcriptomic and protein expression of PCs and IP_3R isoforms was studied by RT-qPCR and Western blot in two PDAC cell lines (PANC-1 and MIA PaCa-2). Their subcellular distribution and colocalization were analyzed by immunofluorescence. Finally, the clinical significance of these expressions was evaluated *in situ* by immunohistochemistry on sections of human pancreatic tumor and non-tumor tissues.
At the cellular level, IP_3R3 was found to be the most highly expressed isoform in PDAC cell lines. Polycystins, particularly PC2, are highly expressed in the most invasive cell line (PANC-1). By immunofluorescence, PC1 is primarily localized to the plasma membrane, while PC2 is localized to the endoplasmic reticulum (ER). Image overlays reveal a close proximity between PC2 and the IP_3Rs at the ER. These results are corroborated *in situ* by IHC, showing overexpression of PC2 and IP_3R3 in tumor areas compared to non-tumor areas.
This study demonstrates the overexpression of PC2 and IP_3R3 in PDAC tumor tissues as well as their cellular proximity within the endoplasmic reticulum. These observations suggest the need for further studies to understand the role of this PC2/IP_3R3 complex and necessitate the conduct of functional studies.

P4 - FUNCTIONAL ROLE OF TETRODOTOXIN-SENSITIVE SODIUM CHANNELS IN CARDIAC AUTOMATICITY

Eliane Morais Pinto[1]; Isabelle Bidaud[1]; Hugo Millet[2]; Sophie Nicole[1]; Michel De Waard[2]; Matteo Elia Mangoni[1]; Jérôme Montnach[2]; Pietro Mesirca[1]

[1]Institut de Génomique Fonctionnelle - CNRS INSERM UMR5203, Université de Montpellier, Montpellier, France.

[2]U1087, l'institut du thorax, INSERM UMR1087, CNRS UMR 6291, Univ Nantes, Nantes, France.

Introduction: Spontaneous rhythmicity (automaticity) of the adult heart is generated in the sinoatrial node (SAN) by a specialized population of myocytes known as pacemaker cells (PMs) able to generate spontaneous periodical oscillations of their membrane potential. Automaticity in PMs is due to diastolic depolarization (DD) a spontaneous slowly depolarizing phase of the action potential cycle. DD results from a complex interaction between intracellular calcium dynamics and sarcolemma ion channels, particularly HCN4 channels, L-type $Ca_v1.3$ channels and T-type calcium channels. While the contribution of these channels to cardiac pacemaking has been extensively investigated, the role of tetrodotoxin-sensitive sodium (TTX-S) channel isoforms is less understood.
Objective: Investigate the functional role of TTX-S channels in cardiac automaticity, using huwentoxin-IV (HwTx-IV), a natural peptide inhibiting selectively TTX-S channels.

Methods: We employed the patch-clamp technique for recording ionic currents and automaticity in isolated PMs in control condition and after perfusion of 100nM HwTx-IV alone and in combination with 50nM TTX. ECG parameters (HR, QT, QRS, T-wave area) were measured in anesthetised rats before and after intravenous injection (iv) of 50µg/kg HwTx-IV. mRNA expression of the TTX-S isoforms was evaluated by RNA sequencing and qPCR experiments in isolated SAN from wild-type mice.

Results: 100nM HwTx-IV induced a significant reduction in sodium current measured in isolated PMs (49% at -25mV). Subsequent application of 50nM TTX did not show any additive effect on current density. AP frequency in isolated PMs was reduced by 13% after perfusion of 100nM HwTx-IV. Consistently, iv injection of 50µg/kg HwTx-IV in anesthetised rats caused 11% reduction in heart rate. RNA sequencing data revealed that among the TTX-S isoforms, $Na_v1.4$ isoform showed the highest expression in SAN. We thus investigated the functional role of $Na_v1.4$ isoform in cardiac pacemaking in isolated PMs from $Na_v1.4$+/- mice. Basal $Na_v1.4$+/- PMs AP rate was 22% lower than AP rate recorded in $Na_v1.4$+/+ PMs.

Conclusion: Our results indicate, for the first time, a previously unappreciated role of the $Na_v1.4$ isoform of TTX-S sodium current in heart automaticity.

P5 - STIM2 VARIANTS REGULATE ORAI1-MEDIATED STORE-OPERATED Ca^{2+} ENTRY AND MITOCHONDRIAL Ca^{2+} HOMEOSTASIS IN CARDIOMYOCYTES

Rui Luo[1]; Pauline Le Gourriérec[1]; Fabrice Antigny[2]; Ana-Maria Gómez[1]; Jean-Pierre Benitah[1]; **Jessica Sabourin[1]**

[1]Inserm, UMR-S 1180, Signalisation et Physiopathologie Cardiovasculaire.

[2]Inserm, UMR-S 1358, Hypertension Pulmonaire: Physiopathologie et Innovation Thérapeutique (HPPIT).

Background: Stromal interaction molecules, STIM1 and STIM2, are SR Ca^{2+} sensors that initiate store-operated Ca^{2+} entry (SOCE). Recently, two STIM2 splice variants have been identified: STIM2.1, an SOCE inhibitor, and STIM2.2, an SOCE activator. The role of STIM1-mediated SOCE has been highlighted in cardiac pathobiology, but the role of STIM2.1 and STIM2.2 is unknown. Aim: To assess whether STIM2.1 and STIM2.2 variants regulate SOCE and their functional role in neonatal rat ventricular cardiomyocytes (NRVMs). Methods: To analyze the function of STIM2.1 and STIM2.2 variants, the NRVMs were transfected with fluorescent-tagged STIM2.1 or STIM2.2 constructs or with STIM2 siRNAs. Results: STIM2 was expressed and formed a complex with Orai1 and STIM1 in NRVMs. Using Ca^{2+} imaging and patch-clamp techniques, we showed that STIM2 knockdown (KD) by siRNAs significantly increased SOCE and JPIII-sensitive I_{SOC} current, strongly suggesting that STIM2.1 is functional in NRVMs. We identified transcript expression of the Stim2.1 and Stim2.2 variants in cardiomyocytes, with a predominance of Stim2.2. Using conventional and super-resolution confocal microscopy (STED), we found that exogenous STIM2.1 and STIM2.2 formed pre-clusters with a reticular organization at rest. Following SR Ca^{2+} store depletion, some STIM2.1 and STIM2.2 clusters translocated to SR-plasma membrane junctions and co-localized with Orai1, suggesting a functional coupling that could imply SOCE regulation. Next, we found that STIM2.1 overexpression suppressed Orai1-mediated SOCE and JPIII-sensitive I_{SOC} current and opposed the STIM2.2-enhanced SOCE effect. These results confirmed an opposite role for both splice variants in regulating SOCE after store depletion. Even if STIM2 KD or splice variant overexpression did not affect cytosolic Ca^{2+} cycling, we observed, using Rhod2/AM Ca^{2+} imaging, that Orai1 inhibition or STIM2.1 overexpression abolished mitochondrial Ca^{2+} uptake (mCa^{2+} uptake). By contrast, the STIM2 KD (that enhances SOCE) significantly increases the mCa^{2+} uptake. We also found that STIM2 was present in mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs) by interacting with IP3Rs, VDAC, MCU, and Mfn2. Conclusion: Our results suggested that, in NRVMs, STIM2.1 constitutes the predominant functional variant that negatively regulates Orai1-generated SOCE. It participates in the control of mCa^{2+} uptake capacity, possibly via the STIM2-IP3Rs-VDAC-MCU and MNF2 complex.

P6 - TRACING SEPARATE EVOLUTIONARY PATHS OF pH, TEMPERATURE AND PRESSURE SENSING IN K2P CHANNELS

Cristina Arrigoni[1]; Marco Destito[1]; Franck C Chatelain[2]; Ali Vafarei Rad[1]; Delphine Bichet[2]; Marco Lolicato[1]

[1]Department of Molecular Medicine, University of Pavia.

[2]Université Côte d'Azur, Centre national de la recherche scientifique, Institut national de la santé et de la recherche médicale, Institut de pharmacologie moléculaire et cellulaire.

Two-pore domain potassium (K2P) channels of the TREK subfamily integrate temperature, mechanical force and extracellular pH to control cellular excitability, yet the evolutionary origins of this polymodal gating remain unclear. Here we combine ancestral sequence reconstruction with electrophysiology to resurrect key vertebrate ancestors of TREK-1, TREK-

2 and TRAAK. All ancestral channels form functional, potassium-selective pores with conserved C-type gating. However, their sensory profiles diverge markedly. We find that temperature responsiveness is an ancestral property of the TREK-1/2 transmembrane core that was subsequently diversified through lineage-specific modifications and amplification by specialized C-terminal domains. In contrast, ancestral TRAAK displays pronounced mechanosensitivity but reduced thermosensitivity. Extracellular acid inhibition emerges as a primordial feature that later diversified via structural remodeling of the outer vestibule. Together, our findings indicate that the channel core functioned as the original sensor of physical and chemical cues, with subsequent evolutionary partitioning of regulatory functions shaping modern K2P polymodality.

P7 - TOWARDS A METABOLIC MASTER KEY TO REVERSE CANCER FATE

Stefano Conti Nibali[1]; Silvia De Siervi[2]; Mostafa H Ahmed[3]; Vito De Pinto[4]; Cristian Turato[2]; Simona Reina[1]; Cristina Arrigoni[2]; **Marco Lolicato[2]**

[1]Department of Biomedical and Biotechnological Sciences, University of Catania, Italy.

[2]Department of Molecular Medicine, University of Pavia.

[3]Atomwise, Inc., San Francisco, CA, USA.

[4]Department of Biomedical and Biotechnological Sciences, Section of Biology & Genetics, University of Catania, Catania, Italy.

The voltage-dependent anion-selective channel isoform 1 (VDAC1) is the major metabolite-conducting pathway of the mitochondrial outer membrane and a key regulator of cellular metabolism and apoptosis. Its altered expression and function in cancer have made VDAC1 an attractive therapeutic target. We recently identified a class of small-molecule VDAC antagonists (VAs) that bind VDAC1 with micromolar affinity and compete with NADH at a partially overlapping binding site.

To determine how VA binding affects channel function, recombinant human VDAC1 was reconstituted into planar lipid bilayers and analyzed by single-channel electrophysiology. VA molecules produced a reproducible reduction in the voltage dependence of VDAC1 gating. Under asymmetric KCl conditions, the drug-bound channel remained predominantly anion selective, indicating that VA binding modifies the permeation properties of the pore and may disrupt both cation fluxes and the transport of negatively charged metabolites.

These biophysical effects were associated with mitochondrial stress and reduced proliferation in cancer cells. In patient-derived intrahepatic cholangiocarcinoma organoids, VA treatment caused a dose-dependent reduction in viability while showing a lower impact on healthy cells than gemcitabine. Together, these findings link ligand binding at a conserved VDAC1 pocket to changes in gating, selectivity, and cancer-cell metabolism, supporting pharmacological modulation of VDAC1 as a potential anticancer strategy.

P8 - ELECTROMECHANICAL CHARACTERISATION OF RABBIT LIVING MYOCARDIAL SLICES AFTER MAINTENANCE IN CULTURE CONDITIONS OR COLD STORAGE

Anthony Coté; Arthur Boileve; Jayce Phillips; Peter Kohl; Ursula Ravens; Rémi Peyronnet
Institute of Experimental Cardiovascular Medicine.

Introduction: Recent advances in culture techniques allow living myocardial slices (LMS) to be maintained viable for several days to weeks. To evaluate their suitability for antiarrhythmic drug screening, we investigated the stability of the electromechanical properties of rabbit atrial and ventricular LMS under two commonly used preservation conditions: 37°C culture conditions (CC) for electro-mechanically active slices, and 4°C cold storage (CS) for excitation-contraction uncoupled slices, each for up to 72h. In addition, we tested the responsiveness of LMS to the antiarrhythmic drug dofetilide.

Methods: Hearts of adult New Zealand White rabbits (70-76 day old) were excised and perfused in Langendorff mode with oxygenated physiological solution at 37°C for 2 min, followed by modified Tyrode's solution containing 2,3-butanedione monoxime (BDM; in mM: NaCl 138, KCl 5.4, HEPES 10, $CaCl_2$ 0.5, $MgCl_2$ 2, glucose 10, NaH_2PO_4 0.33, BDM 30) for 2 min at 37°C, and subsequently stored in this same solution at 4°C. Cardiac tissue was cut with a vibratome into 400 µm thick slices that were placed in biomimetic chambers, preloaded with 1 mN and for CC kept after calcium recovery in culture medium (M199, supplemented with HEPES 10 mM, hydrocortisone 20 nM, penicillin-streptomycin 1:100, insulin-transferrin-selenium 1:100), or for CS in physiological solution (in mM: NaCl 140, KCl 5.4, HEPES 10, $CaCl_2$ 1.8, $MgCl_2$ 1, glucose 10). Action potentials were recorded with sharp microelectrode after 1h of recovery in physiological solution for CS or 15 min for CC. Contractile force was monitored using the chamber's built-in force transducer.

Results and Conclusion: Time-matched action potential parameters and contraction amplitudes from ventricular and atrial LMS did not differ significantly in LMS subjected either to CC or to CS. Dofetilide prolonged atrial action potential duration at 90% of repolarisation in a concentration-dependent manner at 24h of CC and CS, while it increased contraction amplitude only in CC slices. This suggests that CC may be more suitable than CS for maintenance of stable electromechanical properties. Future studies will investigate the mechanisms underlying the lack of inotropic response to dofetilide in CS slices.

P9 - OVEREXPRESSED MECHANOSENSITIVE CHANNELS SYNERGISTICALLY TRIGGER ENDOTHELIAL DYSREGULATION IN CEREBRAL CAVERNOUS MALFORMATIONS

Janne de Jong[1]; Candice Pasquier[2]; Thomas Manicom Ramsamy[2]; Ashraqat Ahmed[3]; Anna Onisiforou[4]; Salim Abdelilah Seyfried[5]; Aubin Penna[6]; Souvik Kar[3]; Hans Van Oosterwyck[1]; **Eva Faurobert[2]**

[1]*KU Leuven, Department of Mechanical Engineering, Leuven, BELGIUM.*
[2]*Institute for Advanced Biosciences, Grenoble, FRANCE.*
[3]*International Neuroscience Institute INI Hannover, GERMANY.*
[4]*Translational Neuropharmacology Laboratory, University of Cyprus, CYPRUS.*
[5]*Institute of Biochemistry and Biology, Potsdam University, Potsdam, GERMANY.*
[6]*CNRS, Université de Poitiers, 4CS, Poitiers, FRANCE.*

Defective cellular sensing and responding to mechanical cues are key drivers of many pathological conditions. In the vasculature, disorders can arise from impaired mechanosensing or transduction of signals such as shear stress, cyclic strain, or wall stiffness. Cerebral cavernous malformations (CCMs) is one such disease where defective cell mechanics combines with genetic defects to give rise to clusters of abnormally dilated, leaky capillaries that invade the brain and are prone to leakage, rupture and hemorrhage. Currently, the only treatment option is surgical excision of symptomatic lesions, but this carries substantial risks, particularly for CCMs in deep brain regions or the brainstem.
How biomechanical forces intersect with genetic defects to drive CCM remains largely unexplored. A striking and unresolved feature of CCMs is their selective formation in low-flow venous capillaries, while high flow appears protective. One plausible explanation is a dysregulation of flow mechanosensing. Here, we demonstrate that the mechanosensitive calcium channels PIEZO1, TRPV2, and TRPV4 are upregulated in ECs bordering CCM lesions in a cohort of 42 patients with TRPV2:TRPV4 expression ratio correlating with the size of lesions. We uncover a functional coupling between the prototypical force sensor PIEZO1 with TRPV4 at cell–cell junctions and with TRPV2 at cell–ECM adhesion sites. Mechanistically, PIEZO1 and TRPV4 destabilize intercellular junctions in a complementary way, while PIEZO1 and TRPV2 jointly promote ECM adhesion, degradation, and invasive behavior. TRPV4 overexpression upregulates the mechanosensitive transcription factors KLF2 and KLF4 and its downregulation or pharmacological inhibition rescues morphogenetic defects in ccm2-mutant zebrafish embryos. Overall, we uncover a previously unrecognized mechanosensitive axis in CCM pathogenesis with TRPV2/TRPV4 as a central hub. We propose that combined pharmacological inhibition of TRPV2 and TRPV4 could restore endothelial barrier integrity while suppressing pathological angiogenesis, thereby reducing lesion burden in CCM patients. Moreover, the TRPV2:TRPV4 ratio emerges as a potential biomarker for disease progression, offering a tool for clinical decision-making and therapeutic monitoring.

P10 - DISTINCTIVE Ca^{2+} HANDLING MODULATION IN A RAT MODEL OF RIGHT HYPERTROPHY AND DYSFUNCTION IN RESPONSE TO MILD OR SEVERE PULMONARY ARTERY CONSTRICTION

Pauline Le Gourriérec[1]; Angèle Boët[2]; Rui Adão[3]; Carmen Brás-Silva[3]; Ana-Maria Gomez[1]; Jean-Pierre Benitah[1]; David Montani[2]; Olaf Mercier[2]; Fabrice Antigny[2]; Jessica Sabourin[1]
[1]INSERM UMR_S1180, Faculté de Pharmacie, Université Paris-Saclay, 91400, Orsay, France.
[2]Université Paris-Saclay, INSERM, UMR_S 1358, Hypertension Pulmonaire : Physiopathologie and Innovation Thérapeutique (HPPIT), AP-HP, Hôpital Bicêtre, Hôpital Marie Lannelongue (Groupe Hospitalier Paris Saint Joseph), ERN-LUNG, FHU André Cournand, Le Plessis-Robinson, France.
[3]RISE-Health, Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, Portugal.

Right ventricular (RV) function is the most important prognostic factor for patients with pulmonary hypertension (PH). Chronically increased afterload from any cause results in right ventricular failure (RVF). However, the pathophysiological mechanisms underlying RVF remain understudied. We assessed the Ca^{2+} dynamics in RV hypertrophy and dysfunction induced by pulmonary artery banding (PAB) in rats to achieve RV overload without affecting the pulmonary vasculature. Using two different degrees of pulmonary artery constriction (mild or

severe), cellular Ca^{2+} imaging was performed on isolated RV cardiomyocytes at 4 weeks post-PAB and sham-operated rats. 4-week mild constriction led to maladaptive RV hypertrophy, with chamber dilation and reduced systolic function, as assessed by echocardiography. The severe constriction accentuated the RV remodelling by increasing the Fulton index and the RV thickness compared to the mild constriction procedure. However, the RV systolic dysfunction level is similar between mild and severe PAB conditions. Transcriptomic analysis in sham and severe PAB rats also identified molecular pathways associated with the maladaptive RV phenotype. In close relationship with these features, the sarcomere became stiffer and generated more force, with a decrease in myofilament Ca^{2+} sensitivity observed only in the severe PAB group. With Fluo-4/AM-based confocal microscopy, we showed that after 4 weeks of mild pressure overload, RV cardiomyocytes had preserved $[Ca^{2+}]_i$ transients amplitude, faster $[Ca^{2+}]_i$ transients decay time, and unchanged sarcoplasmic reticulum (SR) Ca^{2+} load compared to sham myocytes. This was associated with a decrease in cell shortening. After severe pressure overload, RV myocytes exhibited larger and shorter $[Ca^{2+}]_i$ transients and an increased SR Ca^{2+} load, associated with enhanced cell shortening. This was correlated with increased I_{CaL} current. We reveal differences in RV Ca^{2+} handling modulation depending on the degree of pulmonary artery constriction. This finding provides a more comprehensive analysis of the Ca^{2+} dynamics at different stages of RV overload.

P12 - A CRITICAL ROLE OF STIM1 CC1 IN COORDINATING PRODUCTIVE ORAI1 ACTIVATION

Magdalena Prantl[1]; Lara Atzgerstorfer[1]; Marion Reichtomann[1]; Johanna Casata[1]; Verena Steineck[1]; Herwig Grabmayr[1]; Heinrich Krobath[2]; Marc Fahrner[1]

[1]*Institute of Biophysics, JKU Linz.*

[2]*Institute of Theoretical Physics, JKU Linz.*

Store-operated Ca^{2+} entry (SOCE) is the principal mechanism of Ca^{2+} influx in non-excitable cells. It is mediated by the endoplasmic reticulum Ca^{2+} sensor STIM1 and the plasma membrane Ca^{2+} channel Orai1, which together form the Ca^{2+} release-activated Ca^{2+} (CRAC) channel. Tight regulation of this pathway is essential for cellular Ca^{2+} signalling and its dysfunction has been linked to human pathologies like severe combined immunodeficiency (SCID), tubular aggregate myopathy (TAM) and Stormorken Syndrome (STK). Although the major conformational transitions underlying STIM1 activation have been described, the molecular determinants that promote productive STIM1-mediated activation of Orai1 remain incompletely resolved. Here, we examined the contribution of the STIM1 CC1 domain to productive CRAC channel activation by characterizing the conserved residue L265. Therefore, we combined site-directed mutagenesis with electrophysiology, Förster resonance energy transfer (FRET) and molecular dynamics simulations to characterize the structural and functional consequences of perturbing this position. Our data identify L265 as a critical determinant of productive Orai1 activation. Substitution of L265 abolished CRAC channel activity despite preservation of early activation-associated events, indicating that L265 regulates a downstream step required for efficient channel gating. Further experiments suggest that the loss-of-function phenotype results from altered structural organization of STIM1 rather than an intrinsic defect in Orai1 binding. Collectively, these findings suggest a

previously unrecognized regulatory role of the STIM1 CC1 domain in coordinating productive Orai1 activation and provide new mechanistic insight into CRAC channel gating.

P14 - IP3R2-MEDIATED INTER-ORGANELLE Ca^{2+} SIGNALING ORCHESTRATES MELANOPHAGY TO MODERATE SKIN PIGMENTATION

Suman Saurav; Anuradha Jadon; Rajender Motiani
Laboratory of Calciomics and Systemic Pathophysiology.

Human skin pigmentation serves as a crucial defense mechanism against harmful ultraviolet (UV) radiation and dysregulated pigmentation can lead to skin cancers and various pigmentary disorders. Despite its significance, the molecular mechanisms governing pigmentation regulation remain inadequately understood. Here, we focus on elucidating the involvement of inositol 1,4,5-trisphosphate receptor type 2 (IP_3R2) in melanogenesis. Our microarray analysis reveals a correlation between increased pigmentation and heightened IP_3R2 expression. However, the specific role of IP_3R2 in melanogenesis remains unknown. To address this gap, we utilize the LD pigmentation model and employ siRNA-mediated knockdown (KD) techniques targeting IP_3Rs. Our results indicate that IP_3R2 silencing leads to decreased pigmentation, knockdown of IP_3R1 and IP_3R3 does not elicit similar effects. Furthermore, through overexpression experiments, we observe that IP_3R2-M, a mutated form of IP_3R2, exhibits reduced pigmentation compared to wild-type IP_3R2. Intriguingly, despite unchanged mRNA levels of melanogenic regulators (DCT, Tyrosinase, and GP100), protein levels of these regulators are increased upon IP_3R2 KD, suggesting a potential regulatory role of IP_3R2 in melanophagy. Consistent with this hypothesis, our data demonstrates that IP_3R2 KD enhances melanophagic flux. Delving deeper into the mechanism, we explore interorganelle calcium dynamics and find a decrease in mitochondrial calcium levels due to IP_3R2 knockdown, leading to autophagy—a phenomenon reported in several research articles. Remarkably, IP_3R2 knockdown results in increased lysosomal calcium content and decreased pH. This heightened lysosomal Mucolipin1 (MCOLN1) activity facilitates the translocation of transcription factor EB (TFEB) into the nucleus. TFEB, in turn, activates the transcription of key melanophagic genes, inducing melanophagy and ultimately resulting in decreased pigmentation. In summary, our findings shed light on the intricate interplay between IP_3R2-mediated calcium dynamics across organelles and melanophagy. Understanding these mechanisms offers potential therapeutic targets for pigmentary disorders and skin cancers, providing valuable insights for future research in dermatology and oncology.

P15 - ACTIVATION OF IXODES RICINUS MUSCARINIC ACETYLCHOLINE RECEPTOR, MACHR-A, SUGGESTS THE INVOLVEMENT OF AN ENDOGENOUS POTASSIUM CHANNEL IN THE XENOPUS OOCYTES

Philippine Chartier[1]; Alison Cartereau[1]; Emiliane Taillebois[1]; Ladislav Simo[2]; Steeve Thany[1]
[1]*Université d'Orléans, Laboratoire Physiologie, Ecologie et Environnement (P2E), USC INRAE 1328, Orléans, France.*
[2]*ANSES, INRAE, Ecole Nationale Vétérinaire d'Alfort, UMR BIPAR, Laboratoire de Santé Animale, Maisons-Alfort, France.*

Introduction: Ticks are hematophagous ectoparasites transmitting a wide range of pathogens, (including bacteria, viruses, and protozoa), to animals and human. In Europe, *Ixodes ricinus* (the "sheep tick") is the most abundant tick species, and is the vector of at least 20 pathogens, such as the bacteria *Borrelia burgdorferi* responsible for Lyme disease. It has recently been discovered that the salivary glands are controlled by neural projections from the central nervous system, the synganglion, with cholinergic pathways playing a fundamental role. In particular, molecular analyses indicate that *I. ricinus* expresses two pharmacologically distinct muscarinic receptor subtypes, Ir-mAChR-A and Ir-mAChR-B.
Methods: To investigate the pharmacological profiles of tick muscarinic receptors, Ir-mAChR-A was expressed in *Xenopus laevis* oocytes, and currents were recorded using the two-electrode voltage-clamp technique.

Results: Our results indicate that acetylcholine, pilocarpine and bethanecol act as agonists of Ir-mAChR-A, whereas atropine acts as an antagonist. Since potassium channels have been shown to couple with muscarinic receptors to maintain the membrane resting potential and regulate neuronal excitability, we investigated whether Ir-mAChR-A activation involves potassium channels activity. The Ir-mAChR-A was coexpressed with either a human GIRK or an *I. ricinus* Kirk channel. We found that co-expression with species-specific potassium channels is not required for the functional expression and pharmacological properties of tick Ir-mAChR-A. To determine whether Ir-mAChR-A is functionally coupled to an endogenous potassium channel expressed in *Xenopus laevis* oocytes, we used the well-characterized potassium channel blockers, TEA, 4-AP and Cscl. Pre-treatment and co-application of potassium channel antagonists reduced acetylcholine-induced currents, supporting the involvement of endogenous potassium channels in Ir-mAChR-A-mediated responses.

Conclusion: Our results demonstrate that Ir-mAChR-A activation involves endogenous potassium channels in *Xenopus* oocytes.

P16 - REPURPOSING CALCIUM CHANNEL BLOCKERS: A SYNERGISTIC STRATEGY TO OVERCOME THERAPY RESISTANCE IN BRAF-MUTANT METASTATIC MELANOMA

Nadine Ajami[1]; **Sabrina Leverrier-Penna[1]**; Christine Barrault[1]; Margot Krummenacker[1]; Sergio Oterino Sogo[2]; Anouk Senard[1]; Florian Rambow[3]; Ewa Wierzbicka-Hainaut[4]; Christophe Girard[5]; **Aubin Penna[1]**

[1]CNRS, Université de Poitiers, 4CS, Poitiers, France.
[2]Université de Bordeaux, CNRS, IBGC, Bordeaux, France.
[3]Department of Applied Computational Cancer Research, Institute for AI in Medicine (IKIM), University Hospital Essen, Essen, Germany.
[4]Centre Hospitalier Universitaire de Poitiers, Poitiers, France.
[5]INSERM, Université Côte d'Azur, C3M, team 'labellisée Ligue Contre le Cancer 2022', Nice, France.

Metastatic melanoma is the most aggressive form of skin cancer, with the $BRAF^{V600E}$ mutation being the most prevalent genetic alteration. While immune checkpoint inhibitors (ICIs) have transformed treatment paradigms, BRAF/MEK inhibitors (BRAFi/MEKi) remain the standard of care for patients with rapid disease progression or ICI resistance. However, the emergence of

secondary resistance—driven by tumor cell plasticity and non-genetic mechanisms influenced by the tumor microenvironment—limits the long-term efficacy of these therapies.
In our search for molecular drivers of resistance, we uncovered a strong calcium connection. Transcriptome analysis of $BRAF^{V600E}$ melanomas from patients resistant to BRAFi/MEKi revealed a marked activation of cardiac-related calcium signaling pathways. Further investigations demonstrated that BRAFi/MEKi-induced melanoma reprogramming leads to a gradual upregulation of L-type calcium channels (LTCCs), progressing from drug-tolerant persister cells to dedifferentiated cells with acquired resistance. Interestingly, genetic silencing of the CaV1.2 channel in these drug resistant cells resensitized them to targeted therapy-induced cell death.
These findings prompted us to propose and explore a drug repurposing strategy. Preclinical studies demonstrated that targeting LTCCs with calcium channel blockers (CCBs) — a class of antihypertensive drugs — extends tumor response to BRAFi/MEKi *in vivo*. *In vitro* experiments further revealed that CCBs act synergistically with BRAFi/MEKi, ultimately triggering cancer cell death. Mechanistically, CCBs overcome resistance by blocking BRAFi/MEKi-induced activation of the FAK/Akt pro-survival pathway. These results established LTCCs as potential mediators of extracellular matrix-induced resistance.
Overall, our findings support the clinical potential of an innovative drug repositioning strategy, wherein CCBs are used as adjuncts to standard BRAFi/MEKi regimens to improve overall response rates and progression-free survival in patients with metastatic melanoma.

P17 - INVESTIGATING THE ROLE OF THE TRPV1 R772C VARIANT IN SKELETAL MUSCLE FUNCTION AND CALCIUM HOMEOSTASIS: POTENTIAL IMPLICATIONS FOR EXERTIONAL HEAT STROKE SUSCEPTIBILITY

Lucie Maujean[1]; Cassy Enjalbert[1]; Nathan Megret[1]; Camille Blaecke[2]; Ludivine Jaravel[1]; Caroline Benstaali[2]; Stéphanie Chanon[1]; Lionel Augeul[1]; Julien Fauré[2]; **Sylvie Ducreux[1]**
[1]Univ Lyon, CarMeN Laboratory, INSERM, INRA, INSA Lyon, Université Claude Bernard Lyon 1, 69500 Bron, France.
[2]University Grenoble Alpes, Inserm, U1216, CHU Grenoble Alpes, Grenoble Institut Neurosciences, Grenoble.

Exertional heat stroke (EHS) is a severe and potentially fatal syndrome characterized by a core body temperature exceeding 40°C and the development of neurological dysfunction during or following strenuous physical activity. Although EHS predominantly affects young and otherwise healthy individuals, the biological factors underlying individual susceptibility remain incompletely understood. Increasing evidence suggests that genetic determinants involved in skeletal muscle calcium (Ca^{2+}) regulation may contribute to heat intolerance and hyperthermic disorders.
The transient receptor potential vanilloid 1 (TRPV1) channel has emerged as a candidate gene of interest in this context. TRPV1 is a non-selective cation channel activated by noxious heat, protons, and capsaicin. While its role in sensory neurons is well established, TRPV1 is also expressed in skeletal muscle, including the sarcoplasmic reticulum (SR), where it has been proposed to function as a Ca^{2+} leak channel and contribute to intracellular Ca^{2+} homeostasis. A rare missense variant, **R772C**, was recently identified in an individual presenting with EHS,

raising the possibility that altered TRPV1 function may influence susceptibility to exercise-induced hyperthermia.

The objective of the present study was to investigate the impact of the TRPV1 R772C variant on skeletal muscle physiology using a heterozygous knock-in mouse model (**TRPV1$^{R772C+/-}$**). Sedentary male and female mice from three genotypes (**TRPV1$^{+/+}$, TRPV1$^{-/-}$, and TRPV1$^{R772C+/-}$**) were evaluated to distinguish the effects of complete TRPV1 deletion from those associated with the EHS-linked variant. To characterize the role of TRPV1 in skeletal muscle, we analyzed muscle fiber-type composition, assessed intracellular Ca^{2+} handling through measurements of resting cytosolic Ca^{2+} levels and electrically evoked Ca^{2+} transients, and examined the organization of mitochondria-associated membranes (MAMs), specialized contact sites between the SR and mitochondria involved in Ca^{2+} transfer and metabolic regulation.

By exploring the consequences of TRPV1 loss of function and of the R772C variant on muscle phenotype, Ca^{2+} signaling, and SR–mitochondrial interactions, this study aims to provide new insights into the cellular mechanisms that may contribute to genetic predisposition to exertional heat stroke.

P18 - INNOVATIVE AND COMPLEMENTARY STRATEGIES FOR MOLECULAR AND PHARMACOLOGICAL CHARACTERIZATION OF ARTHROPOD NICOTINIC RECEPTORS

Emiliane TAILLEBOIS[1]; Alison[1] CARTEREAU; Steeve H. THANY[1,2]

[1]*Laboratoire Physiologie, Ecologie et Environnement (P2E) USC INRAE 1328, Université d'Orléans.*

[2]*Institut Universitaire de France (IUF), Paris, France.*

Nicotinic acetylcholine receptors (nAChRs) are pentameric receptors involved in rapid neurotransmission. They are crucial for cognitive processes such as learning and memory, and they are the main target of neurotoxic pesticides such as neonicotinoids and their derivatives. Over the past few decades, the adverse effects of pesticides on non-target species, as well as the development of resistance in pests, have highlighted the need to improve our understanding of the functional and pharmacological properties of arthropod neuronal nAChRs. Indeed, the subunits composition of nAChRs is known to influence their pharmacological properties, and consequently the effects of neonicotinoids and their derivatives.

To answer these goals, we develop complementary and innovative multidisciplinary approaches to study arthropod nAChRs : from molecular, cellular and behavioral studies to electrophysiological and molecular modelling approaches.

Microtransplantation of arthropod membrane extracts from the nervous system in *xenopus* ooccyte demonstrate that native nAChRs expressed several nAChR subtypes, and their pharmacological profiles appear different compared to vertebrate nAChRs. Injection of different insect nAChR subunit RNA ratios in the xenopus oocytes demonstrate that several stoichiometries are presents. Using electrophysiology and calcium imaging approaches, we elucidated complex calcium pathways involved in cellular regulation of nAChRs and their sensitivity to pesticides. These studies were conduted on different models with both non-

target species (honeybee, mammals) and target species (aphid, cockroach, ticks) of neurotoxic pesticides to identify species specific differencies.

P19 - EXCITATION–CONTRACTION COUPLING AS A FUNCTIONAL READOUT OF HUMAN IPSC-DERIVED SKELETAL MUSCLE ORGANOID MATURATION

Léa Dorémus[1]; Laura Palmieri[2]; Giorgia Bimbi[2]; Jérôme Piquereau[1]; Sonia Albini[2]; Stéphane Sebille[1]

[1]Laboratoire PRETI, Université de Poitiers, 86073, France.
[2]Genethon, Evry-Courcouronnes, 91000, France.

A key limitation of 3D in vitro models, like human iPSC-derived organoids, is their lack of functional maturity which remains a major challenge in organoid engineering. Several strategies, such as electrical, mechanical or biochemical stimulation, prolonged culture, and co-culture approaches, have been used to promote maturation, with well-regulated calcium handling serving as a key hallmark of successful functional maturation.
In this study, we developed a three-dimensional organoid model based on co-cultures of human induced pluripotent stem cell (hiPSC)-derived skeletal muscle cells and fibroblasts, embedded in a matrigel/collagen hydrogel. We explored two complementary maturation strategies: modulation of fibroblast-muscle interactions, and an optogenetic training protocol using Channelrhodopsin-2 (ChR2) to activate excitation-contraction coupling through repeated light stimulation. The effect of these strategies on maturation was evaluated by analyzing calcium kinetics in response to electrical stimulation, using an automated Python-based pipeline assessing parameters directly reflecting RyR-mediated calcium release and SERCA-dependent reuptake. Both fibroblast co-culture and optogenetic training improved calcium signal quality, with faster release and reuptake kinetics, demonstrating that these strategies enhance the functional maturity in the organoid model.

These results establish hiPSC-derived skeletal muscle organoids as a robust and tunable platform for functional exploration in a human, three-dimensional context. Beyond basic characterization, this matured model opens the way to investigate ion channel-related pathologies, such as Duchenne Muscular Dystrophy, in which calcium homeostasis is disrupted, offering new opportunities for disease modeling and therapeutic target identification.

P20 - ROLE OF TRPM7 KINASE IN THE MODULATION OF GEMCITABINE TRANSPORTER EXPRESSION : INVOLVEMENT IN PANCREATIC CANCER CELL CHEMORESISTANCE.

Laetitia Matias Ramos; Marion Durizy; Mathieu Gautier; Frédéric Hague

CRCLille « Cancer Research Center of Lille » laboratory UMR9020 CNRS – U1366 Inserm – Université de Lille – CHU de Lille – Université de Picardie Jules Verne Team PancResT « Chemoresistance & Therapeutic Targeting in Pancreatic Cancers ».

Pancreatic ductal adenocarcinoma represents the most common form of pancreatic tumors. These tumors are associated with poor prognosis, and their incidence is steadily rising among

patients over the age of fifty. Depending on the patient's health status, the primary therapeutic approach involves the administration of gemcitabine (a pyrimidine antimetabolite). However, patient survival rates remain alarmingly low, standing at only 11% at five years.

Our laboratory findings have highlighted the role of the TRPM7 channel in tumor aggressiveness; indeed, its expression is associated with a poor prognosis (Rybarczyk *et al*., 2012; Auwercx *et al*., 2021). TRPM7 is a membrane cation channel featuring a kinase domain at its C-terminus. While one study suggested that TRPM7 is involved in gemcitabine chemoresistance, no research has specifically investigated the role of its kinase domain in this resistance or in the expression of associated transporters (hENT1 and MRP5) (Yee *et al*., 2012). The aim of our study was therefore to examine the involvement of TRPM7 and its kinase domain in the expression of these factors and in gemcitabine chemoresistance.

Our results suggest that inhibiting the TRPM7 channel or lacking the TRPM7 kinase domain increases the sensitivity of pancreatic cancer cells to gemcitabine. These findings indicate that TRPM7 and specifically its kinase domain plays a role in mechanisms of chemoresistance. Furthermore, we observed that the TRPM7 channel could form membrane protein complexes with gemcitabine transporters (hENT1 and MRP5) and that the TRPM7 kinase domain absence can modulate the expression of these transporters. Thus, our results suggest that the TRPM7 kinase domain may contribute to chemoresistance by modulating the expression of gemcitabine membrane transporters. This modulation appears to rely on a signaling pathway involving the transcription factor CREB.

Collectively, these findings suggest that the TRPM7 kinase domain could serve as a potential therapeutic target to improve patient care by sensitizing cancer cells to chemotherapy.

P21 - UNLOCKING INSECT α7 NICOTINIC ACETYLCHOLINE RECEPTORS: HUMAN–INSECT CHIMERAS REVEAL KEY STRUCTURAL DETERMINANTS OF FUNCTIONAL EXPRESSION

Alison Cartereau1 Chloé Veront[2]; Emiliane Taillebois[1]; Dieudonnée Togbé[2]; Jean-Yves Le Questel[3]; Steeve H. Thany[1]

[1]*Physiologie, Ecologie et Environnement (P2E).*
[2]*INEM.*
[3]*CEISAM.*

Background: The α7 nicotinic acetylcholine receptor (nAChR) is a homomeric ligand-gated ion channel widely studied in vertebrates because of its involvement in neurotransmission, cognition, inflammation, and neurological disorders. In insects, however, α7 receptors remain poorly characterized due to the difficulty of obtaining robust functional expression in heterologous systems. Although human and insect α7 subunits share a close evolutionary relationship, the molecular mechanisms that determine receptor assembly and function are still poorly understood.
Methods: To identify structural elements required for receptor expression and activation, chimeric receptors were generated by exchanging the α7 N-terminal domain between human

and insects, honeybee *Apis mellifera* and cockroach *Periplaneta americana*. Functional expression was assessed in *Xenopus laevis* oocytes using two-electrode voltage-clamp recordings, confocal microscopy, and immunoblotting. Pharmacological characterization was performed using acetylcholine (ACh), α-bungarotoxin (α-Bgt), and the positive allosteric modulator PNU-120596. Mutagenesis analysis of the conserved cys-loop region and homology modelling were used to investigate structural features of the ligand-binding domain.

Results: Chimeric receptors containing the human α7 N-terminal domain formed functional receptors activated by ACh and inhibited by α-Bgt. Human α7 homomeric receptors containing honeybee or cockroach α7 N-terminal domain were expressed at the membrane but remained non-functional. Interestingly, insertion of the human cys-loop into the cockroach α7 N-terminal domain restored receptor functionality, yielding receptors activated by ACh and positively modulated by PNU-120596. Structural modelling revealed a high conservation of the ACh-binding environment among human and insect α7 receptors, suggesting that differences in receptor gating rather than ligand recognition underlie the observed functional disparities.

Conclusions: Our findings identify the human α7 N-terminal domain, and particularly the cys-loop region, as critical determinants of functional receptor expression. These newly characterized human–insect chimeric receptors provide valuable tools for investigating insect α7 pharmacology and may contribute to the development of more selective neuroactive compounds and insecticides.

P22 - A POTASSIUM CHANNEL AS A KEY REGULATOR OF STROMAL PLASTICITY IN PDAC

Léa RIPOCHE[1]; Anette SOUSA DE VEIGA[1]; Raphaël RAPETTI MAUSS[1]; Hélène GUIZOUARN[1]; Claudio MONTENEGRO[2]; Franck BORGESE[1]; Richard TOMASINI[2]; Olivier SORIANI[1]
[1]Université Côte d'Azur, CNRS, INSERM, Institut de Biologie Valrose (iBV), Nice 06108, France.
[2]Cancer Research Center of Marseille (CRCM), CNRS, Aix-Marseille University (AMU), INSERM, Institut Paoli-Calmettes (IPC), 13009 Marseille, France.

Pancreatic Adenocarcinoma (PDAC) is a highly lethal cancer with a 5-year survival rate of under 13%, and is predicted to become the second leading cause of cancer related death in 2030. This tumor is particularly characterized by its aggressive microenvironment, including Cancer Associated Fibroblasts (CAFs), that drive immunosuppression (iCAF), extracellular matrix deposition (myCAFs), thereby enhancing tumor progression. In this context, our team has already identified the SK2 channel in tumor cells as a key driver of CAF-tumor interactions. However ion channels in the CAF compartment have not been investigated yet.
Methods : We developed a bioinformatic pipeline based on public scRNAseq and spatial transcriptomic data to identify relevant ion channels in the stroma. A potassium ion channel (iK) together with two of its regulatory subunits emerged as interesting targets in the CAFs. Working on immortalised patient-derived CAFs, we confirmed iK expression by Western blotting and patch-clamp recordings. Cells depleted for iK (shiK) were characterised by patch clamp experiments and their transcriptomic signatures were analysed by RNAseq together with signalling pathways using phosphoproteomic assays. Finally, CAF differentiation into iCAF

susbet was assessed by IL-1 stimulation followed by IL-6 secretion measurement by ELISA assays.

Results : RNAseq experiments suggest that iK inhibition is associated to a profound remodelling of CAF transcriptional programs, including signatures associated with iCAF, myCAF and ifCAF subsets. Moreover, signalling pathways analysis of shiK showed reduced phosphorylation levels of receptors involved in myCAFs differentiation such as EGFR. Furthermore, shiK CAFs were more sensitive to IL-1 than control CAFs as they secrete twice as much IL-6 following stimulation, indicating a strong impact of iK depletion on CAF responsiveness to their environmental cues. Finally, in silico analysis of scRNA seq data showed different cell lineages based on the expression of auxiliary subunit expression suggesting a role of these subunits in CAF subsets differentiation. Altogether these results show that potassium channels are key regulators of PDAC ecosystem, and targeting iK in the stroma could be an innovative strategy to reduce PDAC aggressiveness.

P23 - EXPLORING THE IMPACT OF ULTRALOCAL TEMPERATURE CHANGE ON Ca^{2+} ION CHANNEL FUNCTION

Tamara Radišković[1]; Maximilian Fröhlich[1]; Yuliia Nazarenko[2]; Susanna Zierler[2]; Evgenii Glushkov[3]; Andrii Yampolskiy[3]; Isabella Derler[1]

[1]Institut für Biophysik/ Abteilung für molekulare Biophysik und Membranbiophysik (Johannes Kepler Universität); Gruberstraße 40, 4020 Linz, Austria.

[2]Institute of Pharmacology (Johannes Kepler Universität); Krankenhausstraße 5, 4020 Linz, Austria.

[3]NanThermix SA, EPFL Innovation Park, 1015 Lausanne Switzerland, NanThermix SA, EPFL Innovation Park, 1015 Lausanne Switzerland.

Temperature is a fundamental physical variable, influencing diverse biological processes ranging from cellular excitability to species migration. In homeotherms, thermosensitive ion channels detect temperature shifts and maintain a stable body temperature and thus prevent tissue damage or even tissue death. Dysregulation of these ion channels is associated with chronic pain, inflammatory diseases, metabolic disorders, and changes in nerve function, making them therapeutic targets. Therefore, clarification of the molecular mechanism underlying temperature-dependent channel gating is essential. Current hypotheses attribute temperature sensitivity to changes in heat capacity and enthalpy, allosteric coupling between sensing domains, or cooperative conformational rearrangements across transmembrane and cytosolic regions. However, no consensus mechanism has emerged, partly due to lack of tools for rapid, spatially localized temperature controls, underscoring the need for more precise experimental evidence. To overcome these limitations, a collaboration with NanThermix SA (Switzerland) was initiated, implementing a fully optical diamond heater-thermometer (DHT) for electrophysiological recordings. This device enables rapid, reversible, and highly localized temperature modulation with simultaneous temperature readout in aqueous environment, allowing precise investigation of thermal effects on ion channel activity. Preliminary data demonstrate that ultralocal heating reversibly modulates currents in several Ca^{2+}-permeable ion channels, which to date have not been shown to be modulated by temperature. Temperature-induced current modulation was detected for both, overexpressed, but also

endogenous channels. By defining temperature-dependent gating mechanisms across ion channels, this work aims to identify pharmacologically tractable strategies that decouple sensory modulation from thermoregulatory effects, thereby advancing the development of safer, ion channel-based therapies.

P24 - MODULATION OF ASIC3 BY LYSO-PAF WITH POTENTIAL INVOLVEMENT IN MUSCLE PAIN

Hélène LUBRANO DI SCAMPAMORTE[1]; Kevin DELANOE[2]; Eric LINGUEGLIA[2]; Fabien MARCHAND[3]; Emmanuel DEVAL[2]

[1]*Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), Sophia-Antipolis.*

[2]*IPMC, Sophia-Antipolis, IPMC, Sophia-Antipolis.*

[3]*Neuro-Dol, Clermont-Ferrand.*

ASICs (Acid-Sensing Ion Channels) are excitatory cationic channels known to be activated by extracellular protons. They are widely expressed in the pain pathway, where they appear as emerging actors in the signalling processes of nociception and pain. Moreover, besides protons, we identified endogenous lipids – such as lyso-phosphatidylcholine (LPC) – as new modulators of ASICs. These lipids are therefore potentially able to alter nociceptive signalling with pathophysiological consequences, and we recently demonstrated a role of LPC in the development of rheumatic pain both in rodents and humans[1].

Here, we investigated the effects of LPC analogues on ASIC3, identifying Lyso-PAF as a potentiator and activator of the channel, while other are inactive. These effects were similar to that of LPC and dependent on extracellular pH. The in vivo effect of one of these analogues was next tested by carrying out pain behavioural experiments on mice, showing that intramuscular injections of this analogue could induce an ASIC3-dependant long lasting secondary mechanical allodynia.

Altogether, these results indicate that beside LPC, other endogenous analogues are also positive modulators or ASICs, and especially ASIC3, which could be important in the pathophysiology of chronic pain arising from deep tissues such as muscle and joint.

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[1]Jacquot, F.; Khoury, S.; Labrum, B.; Delanoe, K.; Pidoux, L.; Barbier, J.; Delay, L.; Bayle, A.; Aissouni, Y.; Barriere, D. A.; Kultima, K.; Freyhult, E.; Hugo, A.; Kosek, E.; Ahmed, A. S.; Jurczak, A.; Lingueglia, E.; Svensson, C. I.; Breuil, V.; Ferreira, T.; Marchand, F.; Deval, E. Lysophosphatidylcholine 16:0 Mediates Chronic Joint Pain Associated to Rheumatic Diseases through Acid-Sensing Ion Channel 3. Pain 2022, 163(10), 1999–2013. https://doi.org/10.1097/j.pain.0000000000002596.

P25- IMPACT OF DIET ON CALCIUM HOMEOSTASIS AND NEUROGENIC ACTIVITY IN NEURAL STEM CELLS OF THE ADULT BRAIN

Michela Crotti[1]; Thomas Harnois[1]; Alexandre Moutet[1]; Marine Coué[2]; Laëtitia Cousin[1]; Nadine Deliot[1]; Luc Pellerin[2]; João Malva[3]; Bruno Constantin[1]; Valérie Coronas[1]

[1]*Laboratoire 4CS UR 22751, 1 rue Georges Bonnet, 86073 Poitiers Cedex 9, University of Poitiers.*

[2]*IRMETIST, INSERM U1313, 1 rue Georges Bonnet, 86073 Poitiers Cedex 9, University of Poitiers.*

[3]*Institute of Pharmacology and Experimental Therapeutics, Faculty of Medicine, University of Coimbra.*

Adult neurogenesis persists throughout life and contributes to memory and cognitive function, emotional regulation, and brain repair capacity. It is sustained by multipotent Neural Stem Cells (NSCs), which proliferate, self-renew, and generate new neurons integrating into pre-existing neural circuits. In the adult mammalian brain, the subventricular zone (SVZ) is the principal neurogenic niche, harboring NSCs that continuously generate neuroblasts, which migrate to the olfactory bulb and participate in odor processing.
SVZ NSCs rely on calcium signalling pathways to maintain their pool and sustain their activity. Our previous studies have shown that these cells express ORAI1, TRPC1, and STIM1, and display store-operated calcium entries (SOCE), which are essential for regulating NSC proliferation and self-renewal. Alterations in SOCE may therefore have profound consequences on NSCs neurogenic activity.

Diet has emerged as regulator of NSC properties and function. Diets high in fat and sugar impair NSC activity by promoting cellular senescence and stem cell exhaustion, thereby accelerating brain aging. Conversely, the Mediterranean diet, rich in anti-inflammatory compounds, antioxidants, and senolytic agents, has been associated with enhanced neurogenesis and reduced age-related cognitive decline. Furthermore, in other cell types, diet has been shown to influence SOCE through various mechanisms including modulation of SOC expression and activity. However, whether dietary interventions affect SOCE in adult NSCs remains largely unexplored.

In this study, we investigated the effects of diet on SOCE and assessed its impact on NSC properties. To this end, NSCs have been isolated from the SVZ of adult mice that had been fed a Western diet (WD, high in fat and sugar) for 14 weeks. Our preliminary results indicate that WD increased STIM1 expression in the SVZ. NSCs isolated from WD-fed mice displayed enhanced SOCE accompanied by increased NSCs proliferation and activation compared with those from chow-fed control mice. These data suggest that WD affects NSC activity through modulation of calcium signalling. Our future work will focus on further investigating these effects and evaluating the ability of compounds found in the Mediterranean diet to rescue WD-induced alterations in NSC neurogenic activity.

P26 - EFFECTS OF PANCREATIC STELLATE CELL ACTIVATION ON CALCIUM SIGNALING.

Clémence MERY DE MONTIGNY[1]; Stéphanie GUENIN[2]; David CROTTES[3]; Lise RODAT-DESPOIX[1]

[1]*CRCLille « Cancer Research Center of Lille » laboratory - UMR9020 CNRS - U1366 Inserm - Université de Lille - CHU de Lille - Université de Picardie Jules Verne - Team PancResT « Chemoresistance & Therapeutic Targeting in Pancreatic Cancers ».*
[2]*Centre Régional de Ressources en Biologie Moléculaire (CRRBM) - Université Picardie Jules Verne.*
[3]*Inserm UMR1069 - Niche Nutrition Cancer & métabolisme Oxydatif (N2COx) - Université de Tours.*

Chronic pancreatitis is an inflammatory disease which constitutes one of the major predisposing factors to pancreatic cancer. The inflammatory process, like the cancerous process, is accompanied by a rearrangement of the pancreatic stroma, called desmoplasia.

This phenomenon leads to a dense fibrotic stroma, activation of Piezo1 mechanoreceptor channel due to high pressure in pancreatic ducts (Swain et *al.*, 2022), and is induced by the activation of pancreatic stellate cells (PSC). In normal pancreas, these support cells are in a quiescent state and participate in tissue and cellular homeostasis. When activated, the PSC acquire a myofibroblastic phenotype and increase tumor aggressiveness by inducing desmoplasia and communicating with cancer cells. These processes could be induced by a modification of calcium signaling, which remains unknown in PSC.
So, the aim of this work is to characterize calcium signaling associated with PSC activation. To this end, various treatments are used to modulate PSC activation: TNF-α (tumor necrosis factor-α) treatment to activate them (Marzoq et *al*., 2019), and ATRA (all-trans-retinoic acid) or JQ-1 (BET inhibitor) treatments to make them quiescent (Froeling et *al*., 2011; Kumar et *al*., 2017). The activation states were confirmed by RNA and protein expressions of the activation marker α-SMA (α-Smooth Muscle Actin), and also by staining lipid droplets with Oil Red O.

Using the Fura-2 calcium fluorescent probe, G protein-dependent signaling pathways were studied by injecting bradykinin or ATP, inducing a significant calcium response with bradykinin and a small response with ATP. Interestingly, stimulation of PSC by Yoda1 or Yoda2, agonists of the Piezo1 mechanoreceptor channel, also induces a high calcium signal. These mechanisms were also investigated depending on the activation states. The effects of Piezo1 inhibition were then compared by using the pharmacological inhibitor Benzbromarone and by siRNA transfections.

P27 - FIELD-MEDIATED VOLTAGE SENSING IN K_2P LEAK CHANNELS: A MEMBRANE-PROXIMAL MECHANISM

Yuval Ben-Abu
Sapir Academic College and Tel Aviv University, Israel.

Two-pore domain potassium (K_2P) channels, classically regarded as voltage-independent "leak" channels, have recently been shown to exhibit robust voltage sensitivity — yet the underlying physical mechanism remains unresolved. We present a theoretical biophysical model in which voltage sensing arises from electrodynamic coupling between permeant K^+ ions and charge-carrying sites within the selectivity filter (SF), without invoking a classical voltage-sensing domain. Our model, accepted in Physical Review E, reproduces the hallmark outward-rectifying and tail-current signatures observed in patch-clamp experiments, and predicts that C-type gating is governed by ion–SF interactions rather than a classical conformational switch. A central hypothesis of this work is that a quantum effect localized near the membrane — such as quantum tunneling or coherent ion–dipole coupling — acts directly on K^+ ions positioned within the ion conduction pathway, thereby modulating the local electrostatic environment and triggering channel opening through a voltage-dependent mechanism. This positions the membrane-proximal region, including the extracellular electrostatic cap of the K_2P pore, as an active quantum transducer rather than a passive structural element. To test this hypothesis, we combine site-directed mutagenesis of predicted ion-interacting residues in the extracellular cap with patch-clamp electrophysiology and molecular dynamics simulations. Together, these three approaches — analytic biophysical

modelling, electrophysiology, and MD — constitute a unifying quantum-electrodynamic account of K^+ channel gating with broad implications across the ion channel superfamily.

P28 - OPTICAL CONTROL OF PIEZO1 MECHANOSENSITIVE ION CHANNELS WITH A TETHERED PHOTOSWITCH: A SINGLE-CHANNEL ANALYSIS OF LIGHT-INDUCED GAIN OF FUNCTION

Antoine LE BRIS
UMR7199 ; Team ICI.

All cells possess the ability to sense mechanical forces and transduce them into biological signals, a process collectively referred to as mechanobiology. PIEZO proteins are mechanically activated ion channels expressed at the cell surface that play critical roles in a wide range of physiological functions, including touch perception, proprioception, blood pressure regulation, and cell differentiation. Moreover, they are implicated in several human pathologies such as hereditary xerocytosis, hypertension, Alzheimer's disease, and mechanical allodynia, making them attractive therapeutic targets.

In this context, we investigated the effects of Maleimide ethylene Azobenzene Trimethyl ammonium (MAT), a photoswitchable compound containing an azobenzene moiety that can be reversibly switched between its *cis* and *trans* configurations and is covalently tethered to the Y2464C mutant of mouse PIEZO1. Tethered MAT specifically opens PIEZO1 upon illumination at 365 nm, which favors the *cis* configuration. Here, we examined how MAT photoisomerization affects mechanically-induced channel activity in the dark.

Using cell-attached patch-clamp recordings in HEK293T cells expressing PIEZO1, we found that mechanically-induced currents were approximately two-fold larger, the inactivation time constant was prolonged, the pressure required to reach half-maximal activation (P50) was reduced, and the slope factor of the Boltzmann fit was decreased following illumination at 365 nm compared with 530 nm, collectively indicating a pronounced gain of function phenotype.

To further investigate the underlying molecular mechanism, we performed single-channel recordings in cell-attached configuration. Transfection conditions and pipette resistance were carefully optimized to isolate individual channels in the membrane. Although technically demanding, single-channel analysis revealed that *cis*-MAT increases the open probability of both fully open state and subconductance open states of PIEZO1 mutant. Strikingly, unitary conductance — reflecting ion permeation through the pore — was not affected, suggesting that MAT modulates gating rather than permeation properties.

These findings provide mechanistic insight into how photochemical tools can selectively modulate PIEZO1 gating and open new perspectives for the development of light-controlled modulators targeting mechanosensitive channels.

P29 - UNEXPECTED ROLE OF $NA_V\beta3$ IN VASCULAR RESPONSE IN FEMALE MICE

Anne-Laure Guihot[1]; Coralyne Proux[1]; Emilie Vessières[1]; Adeline Tailler-Fix[1]; Isabelle Bidaud[1]; Pietro Mersirca[2]; Daniel Henrion[1]; **Claire Legendre[1]**
[1]INSERM, CNRS, MITOVASC, Equipe CarME, SFR ICAT, Univ Angers, Angers, France.
[2]Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, France.

Voltage-gated sodium channels (Na_V), consisting of a pore-forming α-subunit and an auxiliary β-subunit, are well known as key determinants of action potential generation and propagation in excitable cells. Beyond their classical roles in membrane excitability, Na_V channels are implicated in several non-canonical functions, such as in cancer progression. We have recently shown that $Na_V\beta3$ promotes endothelial cell alignment in response to laminar shear stress in vitro, suggesting a potential role in vascular protection.
To further investigate this hypothesis, Scn3b knockout mice were generated from the C57BL/6NTac-Scn3btm1a(KOMP)Wtsi/WtsiH line called $Scn3b^{+/+}$ (WT) and $Scn3b^{-/-}$ (KO). Gene expression analyses confirmed the absence of Scn3b mRNA in the descending thoracic aorta (thAo), mesenteric arteries (MA), and pulmonary arteries (PA) of KO mice. In WT animals, Scn3b expression was highest in PA than MA ($p = 0.0373$) than thAo ($p = 0.0179$). Expression of Scn1b and Scn5a remained unchanged between genotypes, although Scn5a levels were found higher in MA than in thAo or PA. Functional assessment of flow-mediated dilation in isolated MA segments revealed no significant differences between WT and KO mice. Hemodynamic measurements obtained by plethysmography showed similar diastolic blood pressure, pulse pressure, and mean blood pressure across groups. Surprisingly, female KO mice exhibited significantly higher systolic blood pressure than female WT mice (105.3 ± 2.87 vs. 97.16 ± 1.83 mmHg, $p = 0.0314$). Consistently, wire-myography experiments demonstrated enhanced aortic contractile responses to high concentration of phenylephrine exclusively in female KO mice (10^{-5} M, $p=0.0257$; 3.10^{-5} M, $p=0.0133$). Nevertheless, histomorphometric analyses revealed no vascular remodeling in the thAo between WT and KO animals. Interestingly, a potential reduction in the expression of the vasculoprotective genes Klf2 and Nos3 in female KO thAo remains to be confirmed.

Taken together, these preliminary findings suggest a novel and unexpected role for $Na_V\beta3$ in the regulation of vascular function, potentially linked to estrogen-mediated vascular protection that need to be explored by estrogen levels will be measured in $Scn3b^{+/+}$ and $Scn3b^{-/-}$ female mice.

P30 - IMMUNE PROFILING OF MONOCYTES EXPRESSING HUMAN P2X7 SPLICE VARIANTS

Salma Mehafdi; Priska Degro; Barbara Niemeyer; **Dalia Alansary**
Molecular Biophysics Saarland University.

Onset, progression and cardiovascular outcome of chronic kidney disease (CKD) are influenced by the concomitant sterile inflammation. Circulating monocytes and tissue resident macrophages in CKD-associated uremic conditions contribute significantly to the sterile inflammation and to consequent long-term effects such as fibrosis and organ failure. We investigated Ca^{2+} profiles of monocytes from CKD patients which exhibited altered purinergic Ca^{2+} signatures with upregulation of the Ca^{2+} permeant ionotropic ATP receptor P2X7. In

murine CKD models, deleting P2X7 abolished pro-inflammatory cytokines IL-1ß and IL-1a release but increased IL-1a surface presentation by bone marrow derived macrophages (BMDM) resulting in differential effects on immune cell infiltration of injured kidney and heart tissues. Using chimeric mouse lines, we showed that only the chimera harboring $P2X7^{-/-}$ immune cells showed a striking resistance against injury-induced cardiac remodeling. Together, our results added to vast evidence in available literature highlighting P2X7 as a major regulator of inflammatory processes in chronic and autoimmune diseases. However, the outcome of the clinical trials targeting P2X7 remains disappointing with the underlying hampering mechanisms being mainly unknown. Therefore, we were prompted to address whether differential expression and blocker susceptibility of P2X7 splice variants could explain the poor outcome of clinical trials, we cloned the main functional P2X7 human splice variants and used a combination of CRISPR-Cas9 gene deletion and Lenti viral transduction to express individual variants in a human monocyte cell line. We expect a thorough characterization of Ca^{2+} and reactive oxygen species (ROS) signatures mediated by P2X7 splice variants as well as the immune profile of the corresponding monocytes together with a detailed expression analysis to contribute to understanding the yet ambiguous in vivo resistance to treatment with P2X7 blockers and thus improve the treatment strategies and outcome for several inflammatory and autoimmune diseases.

P31 - COMPARATIVE ANALYSIS OF TRPML1 LYSOSOMAL Ca^{2+} CHANNEL ACTIVITY IN IPS-DERIVED MUSCLE CELLS FROM HEALTHY OR DMD PATIENTS.

Marianne Bernard[1]; Léa Dorémus[1]; Matthieu Régnacq[1]; Sonia Albini[2]; Stéphane Sebille[1]
[1]Laboratoire PRéTI, UR 24184, Université de Poitiers, France.
[2]Genethon, 91100 Evry, France.

Duchenne muscular dystrophy (DMD) is caused by dystrophin deficiency and leads to progressive muscle degeneration. A major hallmark of DMD is abnormal intracellular Ca^{2+} homeostasis, involving sarcolemmal instability and altered sarcoplasmic reticulum (SR). Another conserved feature of DMD appears to be lysosomal dysfunction. Beyond their degradative role, lysosomes are signalling hubs for autophagy, membrane repair and metabolic adaptation. The lysosomal channel TRPML1 (MCOLN1) mediates lysosomal Ca^{2+} release and can activate pathways controlling lysosomal biogenesis/autophagy. Although TRPML1 activation has shown benefits in dystrophic mouse models, its regulation and functional output in human skeletal muscle and its contribution to DMD Ca^{2+} dysregulation remain unclear. To fill this gap and specifically analyse the Ca2+ channel activity of TRPML1, we designed a genetically engineered protein calcium probe (GCaMP6) fused to human TRPML1. The probe colocalized with Lamp1 in wild-type (WT) myoblasts, confirming its lysosomal localization. Time-lapse recording revealed a strong fluorescence increase in response to ML-SA5, a selective TRPML1 activator. This fluorescence emission was no longer detected in cells where lysosomes had been permeabilized with Glycyl-L-Phenylalanine-2-Naphthylamide (a cathepsin C substrate). Detailed analysis of the lysosomal Ca2+ release profiles did not reveal any significant differences between WT or DMD myoblasts challenged

with ML-SA5. In contrast, at the myotube stage similar amplitudes of Ca2+ release were observed in WT and DMD cells, but DMD cells exhibited a faster return to basal levels.

P32 - BREAKING THE SOX2-NANOG ALLIANCE: ORAI1 AS A PROTECTIVE BRAKE ON LUMINAL A BREAST CANCER STEM CELLS

Isaac Jardin[1]; Vanesa Jimenez-Velarde[1]; Sandra Alvarado[1]; Javier Garcia-Casado[2]; Tarik Smani[3]; Juan Antonio Rosado[1]

[1]*Department of Physiology (Cellular Physiology Research Group), Institute of Molecular Pathology Biomarkers, University of Extremadura, Extremadura, Spain.*

[2]*Immunology Unit, Department of Physiology, Institute of Molecular Pathology Biomarkers, University of Extremadura, Extremadura, Spain.*

[3]*Department of Medical Physiology and Biophysics, University of Seville, Seville, Spain.*

Store-operated Ca^{2+} entry through Orai channels has emerged as a key regulator of cancer stem cell (CSC) maintenance, but the isoform-specific roles of Orai1, Orai2 and Orai3 in luminal A breast cancer remain unclear [1]. Here we combined CRISPR-modified MCF7 models, siRNA-mediated knockdown and flow cytometry with *in silico* analysis of the TCGA-BRCA luminal A cohort to dissect how Orai isoforms control the pluripotency factors SOX2 and Nanog and their impact on patient outcome [2]. In vitro, Orai1 deficiency (knockout or knockdown) caused a profound loss of SOX2 and a marked upregulation of Nanog, accompanied by a significant enrichment of the $CD44^{+}/CD24^{-}$ CSC-like subpopulation, indicating that Orai1 constrains the expansion of undifferentiated cells. In contrast, Orai3 knockdown enhanced SOX2 and reduced Nanog without significantly modifying the CSC compartment, whereas Orai2 silencing had no detectable effect on pluripotency markers or stemness. *In silico*, ORAI1 expression showed a positive correlation with SOX2, and low ORAI1 levels identified luminal A patients with poorer overall survival, particularly during early follow-up. A combined low ORAI1/SOX2 signature and an ORAI1/SOX2 risk score further refined prognostic stratification, defining a high-risk subgroup with nearly two-fold increased mortality and time-dependent ROC analyses indicating greater discriminative performance at early time points. Altogether, our data reveal a functional decoupling of SOX2 and Nanog that is selectively governed by Orai1-mediated Ca^{2+} signaling in luminal A breast cancer and support a protective role of Orai1 in limiting CSC expansion, cautioning against indiscriminate Orai1 inhibition in this molecular subtype.

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Keywords: Orai1, Orai3, SOX2, Nanog, luminal A breast cancer, cancer stem cells, overall survival.

Corresponding author: Isaac Jardín Polo, ijp@unex.es; https://orcid.org/0000-0003-4575-8264.

P33 - TRPM2 CHANNEL INCREASES CELL VIABILITY OF TRIPLE NEGATIVE BREAST CANCER CELLS FOLLOWING CHEMOTHERAPY THROUGH INCREASED MITOCHONDRIAL ACTIVITY

Mayar Soussi[1]; Hasselsweiller Alice[1]; Gordienko Dmitri[1]; Courmont Evan[1]; Nazıroğlu Ayşenur[2]; Nazıroğlu Mustafa[2]; Le Bourhis Xuefen[1]; Lemonnier Loïc[1]; Cantelmo Anna Rita[3]; **Gkika Dimitra[1]**

[1]Univ. Lille, Inserm, CHU Lille, CNRS, U1366-UMR9020 – CRCLille – Cancer Research Center of Lille, F-59000 Lille, France.

[2]Department of Biophysics, Medical Faculty, Suleyman Demirel University, Isparta, Türkiye.

[3]U1011-eGid, Institute Pasteur de Lille, University of Lille, Inserm, CHU Lille, F-59000 Lille, France.

Triple-negative breast cancer (TNBC) is an aggressive subtype lacking estrogen receptor, progesterone receptor and lacking HER2 overexpression, resulting in limited treatment options and poor prognosis. Although chemotherapy is the standard approach, resistance remains a major clinical challenge. This study investigated the role of Transient Receptor Potential (TRP) channels in chemotherapy resistance using TNBC cell lines (MDA-MB-231, SUM-159PT) and a Luminal A cell line (MCF-7), treated with epirubicin, cyclophosphamide and paclitaxel (ECP). Results demonstrate that TRPM2 emerged as a key modulator of resistance. Its expression was upregulated in ECP-treated TNBC cells, enhancing survival and reducing apoptosis. Inhibition of TRPM2 via siRNA or tatM2NX sensitized cells to chemotherapy by promoting apoptosis and altering mitochondrial calcium uptake and oxidative stress. Furthermore, miR-6791 was identified as a negative regulator of TRPM2, and its overexpression restored chemotherapy sensitivity. These findings suggest that targeting TRPM2 or miR-6791 may improve therapeutic outcomes in TNBC.

P35 - EVOLUTIONARY PREDICTION OF PATHOGENIC VARIANTS AND FUNCTIONAL HOTSPOTS IN L-TYPE CALCIUM CHANNELS

Yakimchyk Alesia; **Liedl Klaus**

University of Innsbruck.

Voltage-gated L-type calcium channels play essential roles in cellular excitability, and genetic variation in their pore-forming α1 subunits contributes to a broad spectrum of neurodevelopmental, endocrine, cardiac, and sensory disorders. However, interpreting the rapidly growing number of variants of uncertain significance (VUS) remains a major challenge. Here, we present an evolutionary modeling framework based on sequence co-variation analysis (EVcouplings) that enables both pathogenicity prediction and functional site discovery in L-type calcium channels. Applied to CACNA1C, the framework accurately classifies pathogenic and benign variants through a KDE-calibrated probabilistic model, providing a scalable approach for clinical interpretation and reclassification of VUS. Applied to CACNA1D, the same evolutionary principles accurately recapitulate established functional regions and prospectively identify previously unrecognized functional hotspots throughout the channel. Electrophysiological characterization of five predicted CACNA1D variants confirmed diverse effects ranging from complete loss of channel conductance to complex gain- and loss-of-function gating phenotypes, while structural modeling provided mechanistic explanations for the observed changes. Together, these studies establish evolutionary co-variation analysis as

a powerful and generalizable approach for both clinical variant interpretation and mechanistic discovery in voltage-gated calcium channels. By enabling rapid assessment of newly identified variants and uncovering previously unknown determinants of channel function, this framework provides a foundation for improved molecular diagnosis and the development of variant-informed personalized medicine for calcium channelopathies.

P36 - GUINEA PIG δβγ-ENAC IS LOCKED IN AN OPEN STATE AND UNCOUPLED FROM REGULATION BY PROTEASES

Rene Lawong; Collins etang Etang; Fabian May; Phillip Vorrat; Oliver Rauh; Mike Althaus
Bonn-Rhein-Sieg University of Applied Sciences, Institute for Functional Gene Analytics, Rheinbach, Germany.

Aim

The epithelial sodium channel (ENaC) plays a key role in salt and water homeostasis in tetrapod vertebrates. There are four ENaC subunits (α, β, γ and δ) which form heterotrimeric αβγ- or δβγ-ENaC assemblies. ENaC activity is tightly coupled to proteolytic processing that removes inhibitory tracts embedded in the extracellular domains of its α- and γ-subunits. The removal of the inhibitory tract from the α-subunit determines baseline activity, while that of the γ-subunit confers maximal channel activity. The presence of the δ-subunit in δβγ-ENaC blunts the effect of proteases, but the mechanism by which subunit assemblies affect ENaC response to proteases is not completely understood. Using ENaC constructs from the guinea pig, we investigated how αβγ- and δβγ-ENaC subunits are processed by proteases and how this processing affected the activity of these ENaC assemblies.

Methods and Results

Guinea pig αβγ- or δβγ-ENaCs were heterologously expressed in *Xenopus* oocytes and their control by extracellular proteases was investigated using protein biochemistry, two-electrode voltage-clamp and patch-clamp electrophysiology. Guinea pig αβγ-ENaC activity was tightly coupled to cleavage of its α- and γ-subunits by the endoprotease furin and extracellular chymotrypsin or trypsin. By contrast, δβγ-ENaC activity was not affected by proteases, despite the removal of its γ-subunit's inhibitory tract by proteases. Experiments using a β_{S521C}-ENaC substitution, which locks ENaC in an open state after exposure to the sulfhydryl-reagent [2-(trimethylammonium)ethyl] methanethiosulfonate bromide (MTSET), demonstrated that guinea pig $\delta\beta_{S521C}\gamma$-ENaCs are almost fully open when expressed in *Xenopus* oocytes. On-cell single-channel patch-clamp recordings confirmed that the open probability of guinea pig δβγ-ENaC is nearly 90%.

Conclusion

These results show that guinea pig δβγ-ENaC is locked in an open state and thereby uncoupled from channel control by proteases.

P37 - IS THE δβγ-ASSEMBLY OF THE EPITHELIAL SODIUM CHANNEL (ENaC) A SODIUM SENSOR IN MAMMALS?

Fynn Zahnow[1]; Gianluca Vogelhuber[1]; Fabian May[1]; Matthew R. D. Cobain[2]; Lars Podsiadlowski[3]; Stephan Maxeiner[4]; Gabriela Krasteva-Christ[4]; José L. Crespo-Picazo[5]; Daniel García-Párraga[5]; **Mike Althaus[1]**

[1]Institute for Functional Gene Analytics, Bonn-Rhein-Sieg University of Applied Sciences, Rheinbach, Germany.
[2]Department of Biological and Environmental Science, University of Jyväskylä, Finland.
[3]Leibniz Institute for the Analysis of Biodiversity Change (LIB), Bonn, Germany.
[4]Institute of Anatomy and Cell Biology, Saarland University, Homburg, Germany.
[5]Research Department, Fundación Oceanogràfic de la Comunitat Valenciana, Valencia, Spain.

Aim: The epithelial sodium channel (ENaC) plays a key role in osmoregulation in tetrapod vertebrates and is a candidate receptor for sodium sensation. There are four ENaC subunits (α, β, γ, δ) which form αβγ- or δβγ ENaCs. Using heterologous expression in *Xenopus laevis* oocytes and two-electrode voltage-clamp and patch-clamp electrophysiology, we found that δβγ-ENaCs have an increased activity, operate under higher extracellular sodium concentrations and show less regulatory constrains compared to αβγ-ENaCs. While αβγ-ENaC is a 'maintenance protein' controlling sodium and potassium homeostasis, δβγ-ENaC might therefore represent a 'stress protein' monitoring high sodium concentrations. The δ-subunit emerged with water-to-land transition of tetrapod vertebrate ancestors. We therefore investigated the evolutionary path of ENaC-coding genes in marine and terrestrial mammals.
Methods and Results: Using bioinformatic analyses of genomic data deposited in the National Center for Biotechnology Information database, we investigated the genes *SCNN1A* (α-ENaC), *SCNN1B* (β-ENaC), *SCNN1G* (γ-ENaC) and *SCNN1D* (δ-ENaC) in Cetartiodactyla, a group comprising even-toed ungulates and the cetaceans (whales/dolphins) which transitioned from terrestrial to marine environments in the Eocene. The genes *SCNN1A*, *SCNN1B* and *SCNN1G* are intact in all 22 investigated cetartiodactylan families. PCR analyses showed the presence of transcripts of *SCNN1A*, *SCNN1B* and *SCNN1G* in kidney and lung tissues of Bottlenose dolphins, highlighting αβγ-ENaC's role as a maintenance protein. While *SCNN1D* is intact in terrestrial Artiodactyla, it is a pseudogene in all 12 investigated cetacean families. Consistent with *SCNN1D* loss, Bottlenose dolphins and Beluga whales did not show behavioural differences to stimuli with or without sodium in seawater-equivalent concentrations. In addition to Cetartiodactyla, we found reduced selection pressure or pseudogenisation of *SCNN1D* in other marine mammals, including pinnipeds and sea otter. A phylogenetic generalised linear mixed model covering the mammal clades that include marine mammal representatives revealed that the probability of a functional *SCNN1D* gene was considerably higher for non-marine mammals than marine mammals.

Conclusions: These data suggest a function of δ-ENaC as a sodium-sensing protein which might have become obsolete in marine mammals after the migration to high-salinity marine environments.

P38 - Na^+-SENSITIVE ION CHANNELS IN HUMAN THP-1 MONOCYTIC CELLS

Oliver Rauh[1]; Sarah Hani Shoushrah[1]; Tim Urbansky[1]; Jurijs Matvejevs[1]; Katrin Richter[1,2]; Mike Althaus[1]

[1]Institute for Functional Gene Analytics, Bonn-Rhein-Sieg University of Applied Science, Rheinbach, Germany.
[2]Department of General, Visceral, Thoracic, and Transplantation Surgery, University of Giessen, Giessen, Germany.

Aim: It is widely recognized that elevated extracellular Na+ concentrations can trigger pro-inflammatory cytokine-release by monocytes, but the mechanisms contributing to the detection of fluctuating extracellular Na+ concentrations remain largely unknown. The epithelial Na^+ channel (ENaC) has been suggested as a Na^+ sensor in immune cells, however, there is limited evidence for ENaC-mediated transmembrane currents in monocytes. We investigated whether functional ENaCs are present in monocytic cells and contribute to pro-inflammatory cytokine release.

Methods and Results: We measured BzATP-induced secretion of pro-inflammatory interleukin (IL)-1β in lipopolysaccharide (LPS) primed monocytic human THP-1 cells in the absence and presence of ENaC pore blockers. IL-1β secretion was greatly reduced by amiloride, benzamil and phenamil. qPCR experiments revealed low expression of the ENaC α- and δ-subunits, while its β- and γ-subunits were not expressed in THP-1 cells and primary human peripheral blood monocytes, thereby excluding a role for αβγ- or δβγ-ENaC assemblies in these cells. To investigate a possible functional role of non-canonical homomeric α- or δ-ENaCs in human monocytes, we performed conventional and planar whole-cell patch-clamp recordings on naïve and LPS-primed THP-1 cells. We measured the response of the transmembrane currents to a change in the extracellular Na^+ concentration from 1 to 125 mM. While small Na^+-mediated inward currents were detected, there was no effect of amiloride or benzamil, suggesting that THP-1 cells do not have functional ENaCs in their plasma membrane under these conditions. However, THP-1 cells exhibit a Na^+-sensitive outward K^+ current. Further kinetic and pharmacological studies together with overexpression in HEK293 cells suggest that this Na^+-sensitive current component is mediated by the voltage-gated K^+ channel Kv1.3.

Conclusion: While the release of IL-1β by monocytes is sensitive to ENaC inhibitors, there is no evidence for ENaC-mediated currents in these cells, suggesting off-target effects of these drugs. Na^+ sensitivity of human monocytes may not necessarily be mediated by an influx of Na^+, but rather indirectly via a Kv1.3-mediated modulation of the membrane potential, which might influence monocyte activation and cytokine release.

P39 - FUNCTIONAL CHARACTERISATION OF A RARE MUTATION IN THE α-SUBUNIT OF THE EPITHELIAL SODIUM CHANNEL DETECTED IN A PATIENT WITH HYPERTENSION

Karen L. Luján López; Nadja Furtwängler; Oliver Rauh ; Mike Althaus

Bonn-Rhein-Sieg University of Applied Sciences, Institute for Functional Gene Analytics, Rheinbach, Germany.

Aim: The epithelial sodium channel (ENaC) is a sodium-selective ion channel typically formed by three subunits (α, β and γ). ENaC plays an important role in transepithelial sodium re-absorption in the renal distal nephron and thereby contributes to the control of blood

pressure. Gain-of-function mutations in ENaC-subunits can lead to the channelopathy Liddle syndrome (secondary hypertension). Chen et al. (2022 DOI:10.1080/00365513.2022.2140454) described a rare α-ENaC mutation in a hypertensive patient, causing the exchange of isoleucine for serine at position 377 (αI377S-ENaC). The functional consequences of this variant on ENaC-activity have not been investigated. This study aimed to functionally characterise αI377S-ENaC using two-electrode voltage-clamp (TEVC) and patch-clamp electrophysiology.

Methods and Results: ENaC cRNAs corresponding to the patient´s genotype (α-ENaC polymorphisms A334 and T663 with and without I377S) were synthesised and injected into Xenopus oocytes. 24 hours after cRNA-injection, ENaC-mediated transmembrane currents were determined by TEVC recordings at a holding voltage of -60 mV and amiloride (100 µM) was employed to determine ENaC-mediated amiloride-sensitive current-fractions (ΔIami). The ΔIami of αI377Sβγ-ENaC-expressing oocytes were ~80% smaller than those of αβγ-ENaC expressing oocytes. On-cell patch-clamp experiments did not reveal significant differences in single-channel conductance between wild-type and mutant channels. TEVC experiments using a βS520C-ENaC substitution, which locks ENaC in an open state after exposure to the sulfhydryl-reagent [2-(trimethylammonium)ethyl] methanethiosulfonate bromide (MTSET), demonstrated that the open probability (PO) of αI377Sβγ-ENaC is ~11% lower compared to the wild type. Consistently, sodium self-inhibition, an ENaC autoregulatory mechanism that reduces ENaC PO, was enhanced in αI377Sβγ-ENaC. Furthermore, surface biotinylation and immunoblotting of epitope tagged ENaCs revealed that αI377Sβγ-ENaC has a reduced membrane abundance in Xenopus oocytes, in comparison to wild type ENaC.

Conclusions: Mutant αI377Sβγ-ENaC showed an overall decreased activity compared to αβγ-ENaC in a heterologous expression system. However, these findings are not compatible with a gain-of-function mutation as expected in Liddle syndrome.

P40 - DUAL TARGETING OF TRPV4 AND TMEM16A FOR CYSTIC FIBROSIS

Razan Orfali[1], Xinya Mi[2], Ali Aleseem[1], Motohiro Nishida[2]

[1]Department of Pharmacology, College of Medicine, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Saudi Arabia.

[2]Department of Physiology, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, 812-8582, Japan.

Abstract: Cystic fibrosis (CF) is a life-limiting genetic disorder characterized by impaired airway hydration, defective mucociliary clearance, and progressive lung disease resulting from dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR). While CFTR modulators have improved outcomes for selected patients, their mutation-specific efficacy and limited accessibility highlight the need for complementary, CFTR-independent strategies to restore airway surface liquid homeostasis. Alternative epithelial ion channels that regulate calcium signaling, chloride secretion, and ciliary activity represent promising therapeutic targets. Eact is a small-molecule activator of the Ca^{2+}-activated chloride channel TMEM16A,

and emerging evidence suggests that it also modulates transient receptor potential vanilloid 4 (TRPV4), a Ca^{2+}-permeable cation channel involved in ciliary beat regulation and epithelial ion transport. However, the molecular basis and functional consequences of this interaction have not been fully elucidated. Here, we utilized an integrated computational and experimental approach to investigate whether Eact directly binds and activates human TRPV4. Structure-based molecular docking identified Eact binding within a known allosteric pocket of TRPV4 associated with channel gating. Molecular dynamics simulations in an explicit lipid bilayer demonstrated stable ligand engagement and increased conformational flexibility in regions linked to channel activation. Binding free-energy analysis supported a favorable interaction profile consistent with agonist-like behavior. Functional validation using whole-cell patch-clamp electrophysiology in TRPV4-expressing HEK293 cells revealed that Eact significantly increased TRPV4-mediated currents compared with baseline, confirming direct channel activation. Together, these findings provide structural and functional evidence that Eact acts as a direct TRPV4 ligand while retaining its activity on TMEM16A. This dual-channel mechanism highlights a CFTR-independent strategy to enhance epithelial ion transport and mucociliary clearance. By integrating molecular modeling with electrophysiological validation, this work supports dual-channel modulation as a translational approach for improving airway function in cystic fibrosis and related respiratory diseases.

P41 - ACTIVATION OF MECHANOSENSITIVE ION CHANNEL PIEZO1 SUPPRESSES CANCER CELL MIGRATION AND FIBROBLAST-MEDIATED MATRIX PRODUCTION IN PANCREATIC DUCTAL ADENOCARCINOMA

Anastasiia Danshyna[1]; Francesca Bianco[2]; Chiara Vaghi[2]; Zoltan Pethö[3]; Giorgia Chinigo[2]; Valerio Farfariello[1]; Alessandra Fiorio Pla[2]; Natalia Prevarskaya[1]

[1]CRCLille Inserm U1366 - Team IonIC.

[2]Turin Cell Physiology (TCP) Lab - University of Turin.

[3]Institute of Physiology II - University of Münster.

Pancreatic ductal adenocarcinoma (PDAC) is characterized by an extensive desmoplastic reaction and progressive tissue stiffening, which affects cancer and stromal cell behaviour. Mechanosensitive ion channel Piezo1 is responsible for sensing mechanical changes within the various tumour tissues, enabling cellular adaptation to the environment; however, its role in PDAC remains not fully understood. Here, using stiffness-tunable hydrogels to mimic the mechanical properties of PDAC tissue, we investigated the potential protective role of Piezo1 in pancreatic cancer cells and fibroblasts.

Activation of Piezo1 with its chemical agonist Yoda1 triggers Ca^{2+} influx in both tumour and stromal cells, with significantly stronger responses on stiff substrates. In Panc1 cells, increased substrate stiffness promoted oscillatory Ca^{2+} signalling. Activation of Piezo1 with Yoda1 reduced oscillation activity on stiff substrates, while its silencing in soft matrices increased it. Functionally, Piezo1 restrained Panc1 cell motility, as channel silencing increased migration on stiff gels, whereas pharmacological activation suppressed migratory activity.

In fibroblasts, activation of Piezo1 reduced collagen deposition, as demonstrated by Sirius Red and CNA35-dtTomato assays, and resulted in downregulation of profibrotic markers, including COL1A1 and ACTA2. Taken together, our results highlight the important role of Piezo1 as a mechanosensitive regulator that attenuates several stiffness-associated tumour-promoting phenotypes in PDAC, including aberrant calcium signalling, cancer cell migration, and fibroblast-driven matrix remodelling.

REGISTERED: CONTACT INFORMATION

Alansary Dalia
dalia.alansary@uks.eu
Homburg
Germany

Althaus Mike
mike.althaus@h-brs.de
Rheinbach
Germany

Andrini Olga
olga.andrini@inserm.fr
Lyon
France

Anissa Bara
aba@sophion.com
Ballerup
Denmark

Arrigoni Cristina
cristina.arrigoni01@unipv.it
Pavia
Italy

Baron Anne
anne.baron@ipmc.cnrs.fr
Sophia Antipolis
France

Ben Abu Yuval
yuvalb@sapir.ac.il
Sderot
Israel

Bernard Marianne
marianne.bernard@univ-poitiers.fr
Poitiers
France

Berrou Mikaël
mberrou@wpi-europe.com
Friedberg
Germany

Bichet Delphine
bichet@ipmc.cnrs.fr
Valbonne
France

Bossi Elena
elena.bossi@uninsubria.it
Varese
Italy

Branchu Théo
theo.branchu@univ-poitiers.fr
Poitiers
France

Brette Fabien
fabien.brette@u-bordeaux.fr
Montpellier
France

Cartereau Alison
alison.cartereau@univ-orleans.fr
Orléans
France

Chartier Philippine
philippine.chartier@univ-orleans.fr
Orléans
France

Chatelain Franck
chatelain@ipmc.cnrs.fr
Valbonne
France

Closson Louis
louis.closson@umontpellier.fr
Montpellier
France

Constantin Bruno
bruno.constantin@univ-poitiers.fr
Poitiers
France

Cote Anthony
anthony.cote@uniklinik-freiburg.de
Freiburg im Breisgau
Germany

Crotti Michela
michela.crotti@univ-poitiers.fr
Poitiers
France

Danshyna Anastasiia
anastasiia.danshyna@univ-lille.fr
Villeneuve d'Ascq
France

Despoix Lise
lise.despoix@u-picardie.fr
Amiens
France

Deval Emmanuel
deval@ipmc.cnrs.fr
Valbonne
France

Diochot Sylvie
diochot@ipmc.cnrs.fr
Valbonne Sophia Antipolis
France

Doremus Léa
lea.doremus@univ-poitiers.fr
Poitiers
France

Ducreux sylvie
sylvie.ducreux@univ-lyon1.fr
Villeurbanne
France

Farfariello Valerio
valerio.farfariello@univ-lille.fr
Villeneuve d'Ascq
France

Faurobert Eva
eva.faurobert@univ-grenoble-alpes.fr
Grenoble
France

Feliciangeli Sylvain
feliciangeli@ipmc.cnrs.fr
Valbonne
France

Feske Stefan
stefan.feske@nyulangone.org
New York, NY
USA

Gaillardon Marvin
marvin.gaillardon@igf.cnrs.fr
Montpellier
France

Girault Alban
alban.girault@u-picardie.fr
Amiens
France

Gkika Dimitra
dimitra.gkika@univ-lille.fr
Villeneuve d'Ascq
France

Grimm Christian Michael
christian.grimm@pharm.ox.ac.uk
Oxford
United Kingdom

Grutter Thomas
thomas.grutter@unistra.fr
Illkirch
France

Guca Ewelina
ewelina.guca@medchemexpress.com
Nîmes
France

Guse Andreas H.
guse@uke.de
Hamburg
Germany

Hammes Annette
hammes@mdc-berlin.de
Berlin
Germany

Hasselsweiller Alice
alice.hasselsweiller.etu@univ-lille.fr
Lille
France

Hilaire Cecile
cecile.hilaire@umontpellier.fr
Montpellier
France

Hof Thomas
thof@harvardbioscience.com
Oullins Perre Benite
France

Hoppe Leonie
leho00011@uni-saarland.de
Homburg
Germany

Jaime-Tobon Lina Maria
lina-maria.jaime-tobon@inserm.fr
Montpellier
France

Jardin Isaac
ijp@unex.es
Cáceres
Spain

Jaślan Justyna
Justyna.Jaslan@lmu.de
München
Germany

Kaaki Sara
sara.kaaki@univ-orleans.fr
Orléans
France

Kempf Yasemin Aylin
yaseminaylin.kempf@h-brs.de
Rheinbach
Germany

Kondratskyi Artem
Artem.Kondratskyi@nanion.de
Munich
Germany

Lasmarrigues Romane
romane.lasmarrigues@medchemexpress.com
Paris
France

László Csanády
csanady.laszlo@semmelweis.hu
Budapest
Hungary

Lawong Rene
rene.lawong@phd.h-brs.de
Rheinbach
Germany

Le Gourriérec Pauline
pauline.le-gourrierec@universite-paris-saclay.fr
Paris
France

Le-Bris Antoine
antoine.le-bris@etu.unistra.fr
Strasbourg
France

Legendre Claire
claire.legendre@univ-angers.fr
Angers
France

Lelievre Quentin
quentin.lelievre@etu.univ-cotedazur.fr
Nice
France

Lemonnier Loïc
loic.lemonnier@univ-lille.fr
Villeneuve d'Ascq
France

Leverrier-Penna Sabrina
sabrina.penna@univ-poitiers.fr
Poitiers
France

Liedl Klaus
Klaus.Liedl@uibk.ac.at
Mils
Austria

Liu Qiang
qiangliu@cityu.edu.hk
Kowloon Tong
Hong Kong

Lolicato Marco
marcogaetano.lolicato@unipv.it
Pavia
Italy

Lory Philippe
philippe.lory@igf.cnrs.fr
Montpellier
France

Lubrano di Scampamorte Hélène
hlubrano@ipmc.cnrs.fr
Valbonne
France

Luján López Karen Lizet
karen.lujanlopez@h-brs.de
Bonn
Germany

Malecot Lionel
malecot.l@micromecanique.fr
St Germain en Laye
France

Manicom Ramsamy Thomas
thomas.manicom-ramsamy@univ-grenoble-alpes.fr
Grenoble
France

Marti-Solans Josep
josep.marti-solans@obs-banyuls.fr
Banyuls dur Mer
France

Matias Ramos Laetitia
laetitia.matias.ramos@u-picardie.fr
Amiens
France

Méry de Montigny Clémence
clemence.mery.de.montigny@u-picardie.fr
Amiens
France

Mesirca Pietro
pietro.mesirca@igf.cnrs.fr
Montpellier
France

Monteil Arnaud
arnaud.monteil@igf.cnrs.fr
Montpellier
France

Mony Laetitia
laetitia.mony@ens.fr
Paris
France

Morais Pinto Eliane
eliane.morais-pinto@igf.cnrs.fr
Montpellier
France

Motiani Rajender
Rajender.motiani@rcb.res.in
Faridabad, Haryana
India

Mugnier Jean Louis
jemug@univ-smb.fr
le Sappey en Chartreuse
France

Niemeyer Barbara A.
barbara.niemeyer@uks.eu
Homburg
Germany

Orfarli Razan
rsorfali@imamu.edu.sa
Riyadh
Saoudia Arabia

Parsons George
G.Parsons4@newcastle.ac.uk
Newcastle Upon Tyne
United Kingdom

Pathak Medha
medhap@uci.edu
Irvine, CA
USA

Penna Aubin
aubin.penna@univ-poitiers.fr
Poitiers
France

Perrier Marie
marie.perrier@cea.fr
Grenoble
France

Peyronnet Remi
remi.peyronnet@uniklinik-freiburg.de
Freiburg im Breisgau
Germany

Pigelet Luca
pigelet@ipmc.cnrs.fr
Valbonne
France

Prantl Magdalena
magdalena.prantl@jku.at
Linz
Austria

Prevarskaya Natalia
sandy.despeghel@inserm.fr
Villeneuve d'Ascq
France

Pusch Michael
michael.pusch@ibf.cnr.it
Genova
Italy

Radiskovic Tamara
tamara.radiskovic@jku.at
Linz
Austria

Rapetti-Mauss Raphael
Raphael.Rapetti-Mauss@univ-cotedazur.fr
Nice
France

Rauh Oliver
oliver.rauh@h-brs.de
Rheinbach
Germany

Ribeiro de Oliveira Barbara
barbara.ribeiro@inserm.fr
Nantes
France

Ripoche Lea
lea.ripoche@univ-cotedazur.fr
Nice
France

Rosado Juan Antonio
jarosado@unex.es
Cáceres
Spain

Rougier Jean-Sébastien
jean-sebastien.rougier@unibe.ch
Bern
Switzerland

Sabourin Jessica
jessica.sabourin@universite-paris-saclay.fr
Orsay
France

Saurav Suman
suman.saurav@rcb.res.in
Delhi
India

Sebille Stéphane
stephane.sebille@univ-poitiers.fr
Poitiers
France

Sedeño Juan Manuel Gómez
zs24025286@estudiantes.uv.mx
Veracruz
México

Seryshev Alexander
Alexander.Seryshev@uth.tmc.edu
Houston
USA

Serysheva Irina
irina.i.serysheva@uth.tmc.edu
Houston
USA

Shoushrah Sarah
sarah.shoushrah@h-brs.de
Bonn
Germany

Solinas Eleonore
eleonore.solinas@univ-lille.fr
Villeneuve d'Ascq
France

Song Long-Sheng
long-sheng-song@uiowa.edu
Iowa City
USA

Soriani Olivier
olivier.soriani@univ-cotedazur.fr
Nice
France

Supaweera Nassareen
nassareen.sp@mail.wu.ac.th
Montpellier
France

Tabak Joel
j.tabak@exeter.ac.uk
Exeter
United Kingdom

Taillebois Emiliane
emiliane.taillebois@univ-orleans.fr
Orleans
France

Thireau Jerome
jerome.thireau@inserm.fr
Montpellier
France

Torres Estefania
estefania.torres-ortiz@univ-cotedazur.fr
Nice
France

Typou Alexandra
alexandra.typou@igf.cnrs.fr
Montpellier
France

Villagomez Jason

jvi@sophion.com
Ballerup
Denmark

Voisin Pierre

pierre.voisin@univ-poitiers.fr
Poitiers
France

Weidel Petra

petraweidel@t-online.de
Chauvigny
France

Wood John

j.wood@ucl.ac.uk
London
United Kingdom

Yakimchyk Alesia

Alesia.Yakimchyk@uibk.ac.at
Völs, Tirol
Austria

USEFUL INFORMATION

The attendees are expected on Sunday, between 4 PM and 7 PM. During this period, they would have time to check in and meet each other before a welcome drink and dinner. 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 set up for sharing a taxi or a car (personal or rental). You will find this forum under your session (https://www.canaux-ioniques.fr/index.php/my-meeting/forum-for-transportation).

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

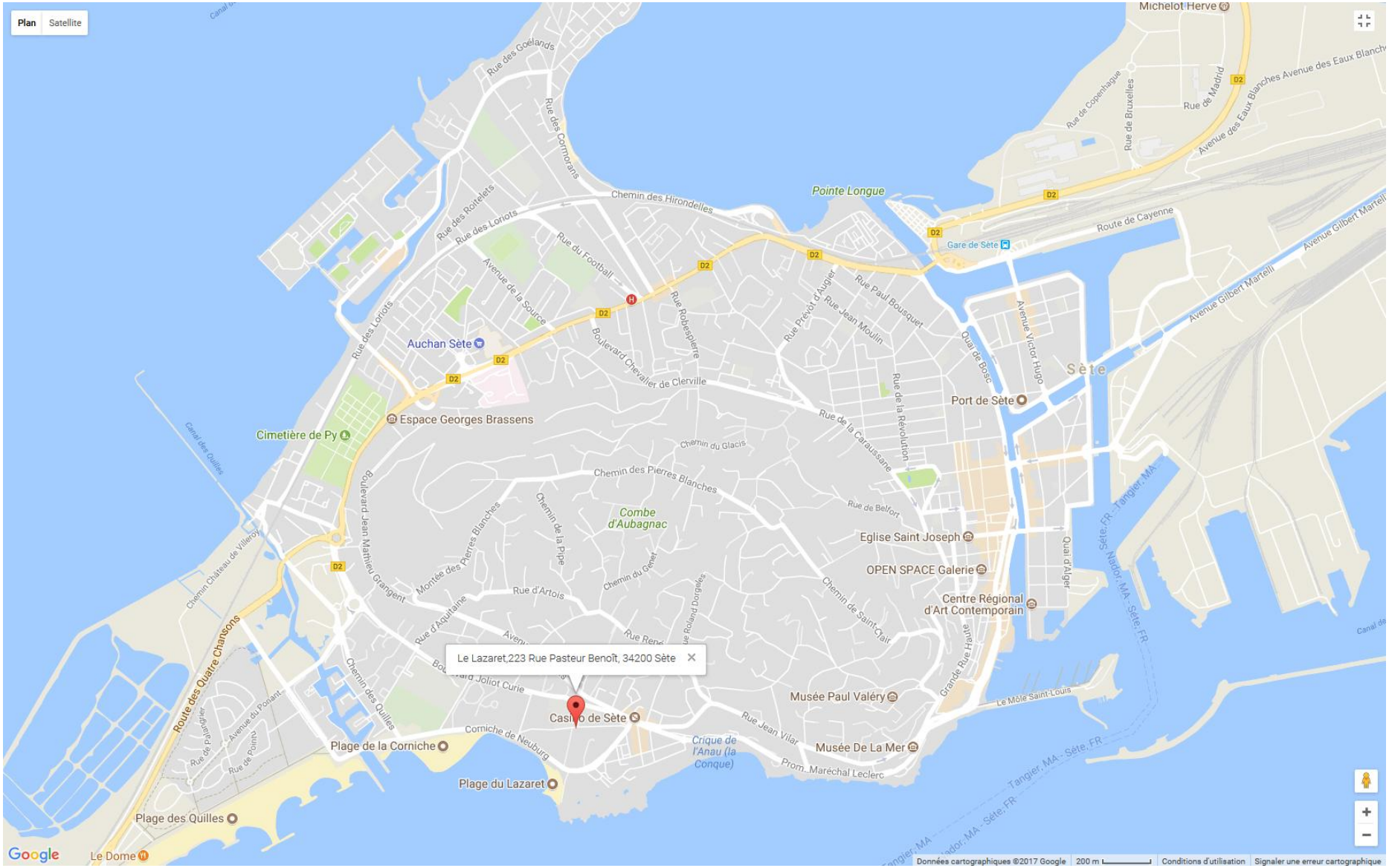
ARRIVING

By Air:
Montpellier Méditerranée Airport is the closest airport. Upon your arrival, you will find a 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. Upon your arrival, you can find taxis and public transportation. For the city bus, take the n°3 line, which operates to the Center Malraux, and stop at the halt "Plan de la Corniche". Alternatively, you can take bus n°9, which operates to Marseillan Plage, and stop at the halt "Le Lazaret". You can check for timetables, directions, and prices at the following web address: https://www.mobilite.agglopole.fr/

By Car :

Free parking is available at the center of "le Lazaret".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Casino de Sète
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Plage du Lazaret
Plage des Quilles
Le Dome
Combe d'Aubagnac
Crique de l'Anau (la Conque)
Route des Quatre Chansons
Boulevard Jean Mathieu Grangent
Boulevard Chevalier de Clerville
Rue des Goélands
Rue des Cormorans
Chemin des Hirondelles
Rue des Roitelets
Rue des Loriots
Rue du Football
Avenue de la Source
Rue Robespierre
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
Montée des Pierres Blanches
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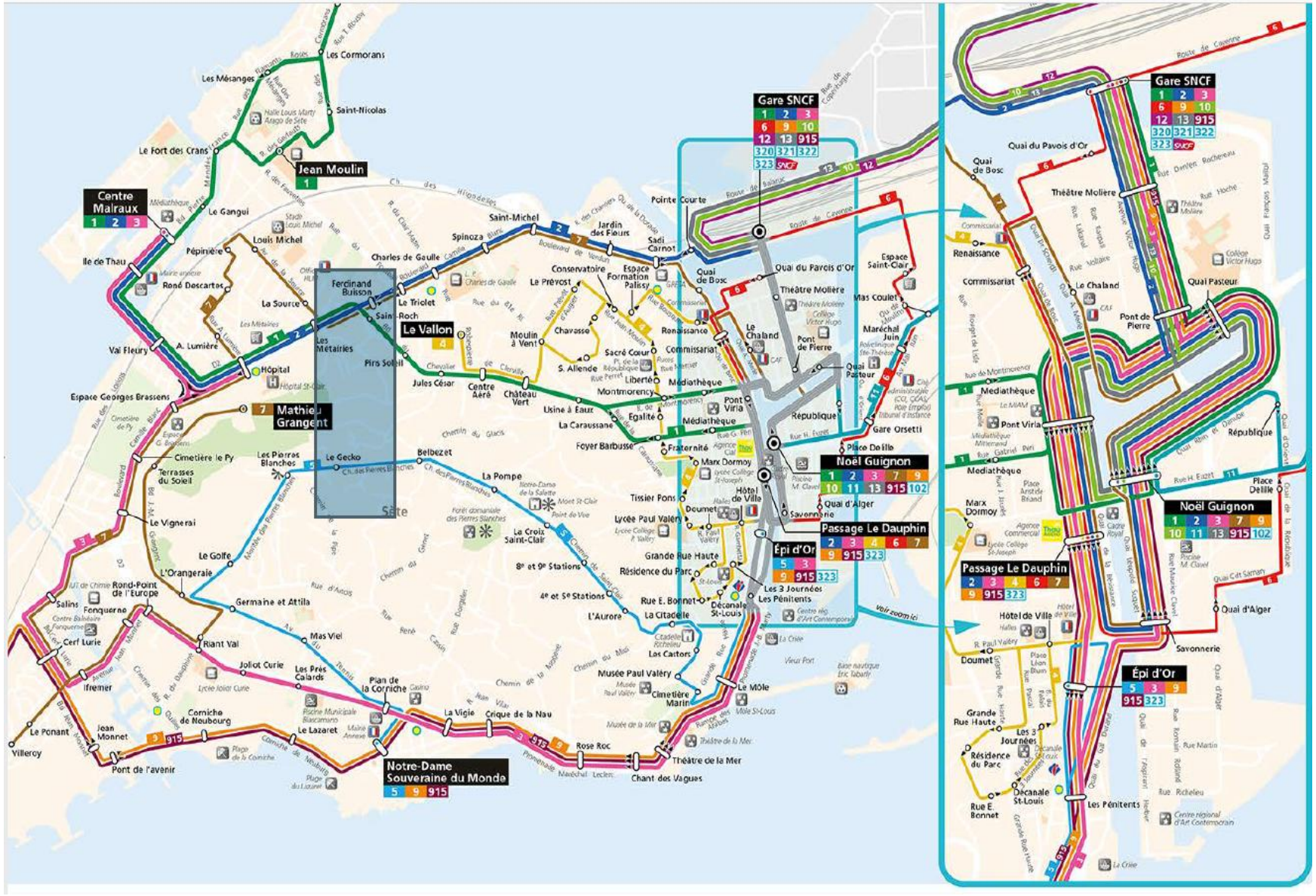
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Épi d'Or
5 3
9 915 323
Notre-Dame Souveraine du Monde
5 9 915
Sète
Le Fort des Crans
Les Cormorans
Les Mésanges
Saint-Nicolas
Le Gangui
Ile de Thau
René Descartes
Pépinière
Louis Michel
Ferdinand Buisson
La Source
Le Triolet
Saint-Roch
Charles de Gaulle
Spinoza
Saint-Michel
Jardin des Fleurs
Sadi Carnot
Pointe Courte
Conservatoire
Espace Formation Paléssy
Le Prévost
Chavasse
Moulin à Vent
S. Allende
Sacré Cœur
Liberté
Renaissance
Commissariat
Quai de Bosc
Quai du Pavois d'Or
Théâtre Molière
Mas Coulet
Le Chaland
Pont de Pierre
Maréchal Juin
Quai Pasteur
Espace Saint-Clair
Vai Fleury
A. Lumière
Les Métairies
Hôpital
Piris Soleil
Jules César
Centre Aéré
Château Vert
Usine à Eaux
La Caraussane
Foyer Barbusse
Egalité
Fraternité
Montmorency
Médiathèque
Pont Viria
République
Gare Orsetti
Place Delille
Marx Dormoy
Hôtel de Ville
Tissier Pons
Doumet
Savonnerie
Quai d'Alger
Espace Georges Brassens
Cimetière le Py
Terrasses du Soleil
Les Pierres Blanches
Le Gecko
Belbezet
La Pompe
Le Vignerai
Le Golfe
L'Orangerale
Rond-Point de l'Europe
Salins
Fonquerne
Cerf Lurie
Ifremer
Riant Val
Joliot Curie
Lycée Joliot Curie
Les Prés Calards
Germaine et Attila
Mas Viel
Plan de la Corniche
Corniche de Nouboug
Le Ponant
Jean Monnet
Villeroy
Pont de l'avenir
Le Lazaret
La Vigie
Crique de la Nau
Rose Roc
Théâtre de la Mer
Chant des Vagues
Le Môle
Musée Paul Valéry
Cimetière Marin
Les Castors
Citadelle Richelieu
L'Aurore
La Citadelle
Rue E. Bonnet
Décanale St-Louis
Les 3 Journées
Les Pénitents
Résidence du Parc
Grande Rue Haute
8e et 9e Stations
4e et 5e Stations
Lycée Paul Valéry
Le Croix Saint-Clair
Forêt domaniale des Pierres Blanches
Notre-Dame de la Salette
Mont St-Clair
Point de Vue
Voir zoom ici
Centre régional d'Art Contemporain
La Criée
Vieux Port
Base nautique Eric Tabarly

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 lines between the Sète SNCF railway station and the Lazaret are lines 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

Others activities

https://www.tripadvisor.fr/Attractions-g660465-Activities-Sete_Herault_Occitanie.html