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► **To cite this version:**

Valérie Coronas, Marie Demion, Ines Elbini, Adèle Faucherre, Alban Girault, et al.. The 33 rd Ion Channels Meeting, September 2024, Sète, France. *Bioelectricity*, 2025, 7 (1), pp.105-111. <10.1089/bioe.2024.0050>. <hal-04910050>

HAL Id: hal-04910050

<https://hal.science/hal-04910050v1>

Submitted on 7 Nov 2025

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The 33rd Ion Channels Meeting, September 2024, Sète, France

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Abstract

The 33rd Ion Channels Meeting has been held in Sète, France, from September the 8th and the 11th. The congress gathered together senior and junior researchers from almost all over the world working on different fields of biology and pathophysiology.

The colloquium opened with the plenary lecture on the action mechanisms of $\alpha 2\delta$ proteins in the trafficking of calcium channels and how these proteins can modulate the channels functional properties, given by Prof. Annette Dolphin.

The five symposia of this edition were focused on several techniques for studying ion channels and their environment, but also on ion channels and their involvement in cancer. Two symposia have been totally dedicated to genetic channelopathies and the last one was devoted to glutamate receptors. All the presentations of the symposia are reported, summarised, in this report meeting article.

Introduction

The Ion Channels Meeting is an international scientific congress that takes place every year in France since 1989, gathering together senior and junior researchers working on different fields of biology (neurosciences, stem cells, hypoxia, cardiac physiology, etc.) and pathophysiology (cancer and metastases, autism, neuromotor and cardiac disorders...) but having as common denominator the ion channels.

The three days of congress were dedicated to scientific exchanges and constructive discussions, allowing young and experienced researchers to benefit from a privileged opportunity to interact with scientists internationally recognized in their field of research.

The 2024 edition grouped 117 participants coming from 15 countries (Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, Spain, Switzerland, Taiwan, The Netherlands, Tunisia, United Kingdom, USA) and 45 abstracts were submitted.

47 This year, celebrating the 33rd edition of the meeting, the scientific committee organized five
48 thematic symposia, each consisting of three talks given by internationally renowned speakers
49 and one talk given by a young researcher selected from the submitted abstracts.

50 As a new feature in the 2024 edition, two of the five symposia have been totally dedicated to
51 genetic channelopathies.

52 Two 'oral communication' sessions have been arranged to give the opportunity to eight
53 additional young researchers to present their work.

54 Two poster sessions (together with a one-minute oral presentation) were included in the
55 program. The two best posters and the best oral presentation from young researchers have
56 been awarded on the last day of the meeting.

57 The meeting has been an opportunity to discover and discuss newly-developed models (in
58 silico, in vitro, in vivo) and technologies that enhance understanding of ion channels, from
59 structure to physiological roles, and foster the development of innovative therapeutic
60 strategies.

61

62 **Plenary lecture**

63 The colloquium opened with the plenary lecture, entitled 'Drugs and trafficking: lessons from
64 calcium channels' given by Prof. Annette Dolphin, from University College London (UCL,
65 London, UK), one of the most representative figures in the field of neuronal voltage gated
66 calcium channels.

67 Her career was mainly devoted to the study of the implication of N-type voltage-gated calcium
68 channels (CaV2.2) and their auxiliary subunits $\alpha 2\delta$ -1 and β in presynaptic neurotransmitter
69 release and, in particular, to their role in primary afferent terminals in the pain pathway.

70 Dolphin's speech focused on the action mechanisms of $\alpha 2\delta$ proteins in the trafficking of
71 calcium channels and how these proteins can modulate the channels functional properties.

72 Changes in CaV2.2 trafficking and function generally go hand-in-hand, but, as she showed, this
73 is not always the case, for example if $\alpha 2\delta$ pre-proteins are not proteolytically cleaved to form
74 the mature $\alpha 2\delta$ protein, and for certain splice variant combinations of CaV2.2. Furthermore,
75 $\alpha 2\delta$ -1 is a drug target in the treatment of neuropathic pain, being the therapeutic binding site
76 for gabapentinoid drugs. Prof. Dolphin identified a key mechanism of action: by binding to
77 $\alpha 2\delta$ -1 (and $\alpha 2\delta$ -2), gabapentinoid drugs induce a reduction in forward trafficking to the cell
78 surface of both $\alpha 2\delta$ and the CaV2 complexes containing $\alpha 2\delta$. In vivo, pregabalin inhibits $\alpha 2\delta$ -
79 1 trafficking in the pain pathway. Furthermore, the $\alpha 2\delta$ -1 increase that occurs following
80 neuropathic injury promotes CaV2.2 trafficking in specific neurons in the dorsal horn.
81 Interestingly, the binding of gabapentinoid drugs to $\alpha 2\delta$ -1 can be disrupted by a mutation
82 [R241A in $\alpha 2\delta$ -1], which is part of a universal amino acid binding pocket, that is conserved in
83 bacterial chemoreceptors, and into which gabapentinoid drugs bind. The physiological role of
84 the amino acid binding site in $\alpha 2\delta$ proteins is still unclear, but since the R to A mutations
85 reduce $\alpha 2\delta$ -1/2 function as calcium channel subunits, binding of endogenous amino acids may
86 be important for their optimal function, possibly occupying the binding site as positive
87 modulators. In contrast, gabapentinoids appear to be negative regulators of $\alpha 2\delta$ function.

88

89 **Symposium 1**

90 **Techniques for studying ion channels and their environment (organized by Jérôme Thireau,**
91 **Laboratoire de Physiologie et Médecine Expérimentale, CNRS-UMR 9214, INSERM U1046,**
92 **Montpellier, France).**

93 Ion channels play a crucial role in cellular physiology, controlling key processes like neuronal
94 function, synaptic neurotransmission, muscle contraction, and even metabolism.
95 Understanding these complex structures and their surrounding environment is vital for
96 grasping their functions, their role in various diseases, and for developing novel therapeutic
97 strategies. Using detailed examples from the speaker's body of work, this symposium explored
98 the cutting-edge techniques used to study ion channels, from traditional electrophysiological
99 approaches to modern advancements in imaging and molecular biophysics.

100 Dr. Laetitia Mony (Institut de Biologie de l'ENS, Paris, France) opened the session with a
101 presentation titled "Combined Approaches to Reveal the Surprising Role of Ion Channels in
102 the Brain". She highlighted the unusual properties of GluD1 receptors compared to traditional
103 ionotropic glutamate receptors (iGluRs). Unlike typical iGluRs, GluD1 receptors bind D-serine
104 and glycine instead of glutamate. Their lack of ionotropic activity in response to agonist
105 binding has made them difficult to thoroughly characterize using conventional
106 pharmacological and biophysical methods. To address this challenge, Mony's team
107 engineered a "Lurcher" mutant that renders the GluD1 channel constitutively open. Using
108 voltage-clamp fluorometry—a fluorescence-based technique for real-time monitoring of
109 receptor conformational changes—they studied isolated GluD1 ligand-binding domains. This
110 revealed that GluD1 also binds the inhibitory neurotransmitter GABA. By combining these
111 approaches with structural analysis and biochemistry, they discovered that GluD1 enhances
112 GABAergic synaptic currents in the adult mouse hippocampus through a non-ionotropic
113 mechanism. This mechanism requires GABA binding (but not D-serine) and trans-synaptic
114 anchoring. Through her presentation, Dr. Laetitia Mony thus introduced a novel form of
115 inhibitory synaptic plasticity dependent on GluD1 receptors.

116 The second invited speaker, Dr. Scott Hansen (Department of Molecular Medicine, The
117 Wertheim UF Scripps Institute, University of Florida Health, USA), delved into the critical role
118 of the lipid environment in ion channel activity and function in his talk, "Techniques to Study
119 Membrane Mechanisms of Disease: Roles of Lipids". Through a comprehensive overview of
120 his research, Dr. Scott Hansen demonstrated how ion channels transit between different
121 membrane compartments as —cholesterol-dependent ganglioside-enriched thick domains
122 and cholesterol-independent polyunsaturated lipid-rich thin domains—, where their
123 functional states are regulated by the surrounding lipid environment. He introduced a cutting-
124 edge super-resolution imaging technique that tracks the movement of a GFP-tagged ion
125 channel (TREK-1) and immunolabeled GABA_A receptors (GABA_{AR}) between these lipid
126 compartments using fluorescently labeled lipids in response to various stimuli. This technique
127 revealed that polyunsaturated fatty acids and shear forces displace TREK-1 channels from
128 thick membrane domains, prompting their migration to thin membranes where they are
129 activated by both exposure to PIP2 clusters and the thin membrane environment. Dr Scott
130 Hansen further explained how GABA application to GABA_{AR}s leads to their dissociation from
131 ordered lipids domains, prompting their migration to PIP2 clusters, a movement correlated
132 with state-dependent changes in current and desensitization. He presented findings on how
133 ion channel movement in neurons is regulated by astrocyte-derived cholesterol through an

134 apolipoprotein E (apoE)-dependent mechanism. Finally, he demonstrated that loading
135 neurons with cholesterol *via* apoE mimics an inflammatory state and triggers neuronal
136 hyperexcitability, underscoring the profound influence of lipid environments on ion channel
137 behavior and neuronal function.

138 The third speaker, Dr. Lucie Bergdoll (Laboratoire d'ingénierie des Systèmes
139 Macromoléculaires, LISM, University of Aix-Marseille, CNRS, UMR7255, Marseille, France),
140 illuminated the role of a key mitochondrial protein, VDAC (Voltage-Dependent Anion
141 Channel). She began by reviewing how the oligomerization of VDAC channels can regulate
142 mitochondrial physiology, acting as gatekeepers that control the exchange of ions and
143 metabolites between mitochondria and the cytoplasm. Dr. Lucie Bergdoll presented her
144 group's use of atomic force microscopy to explore how specific lipids in the mitochondrial
145 outer membrane (MOM) influence VDAC assemblies. She revealed that VDAC forms lipid-
146 sensitive clusters, which they termed "honeycombs." The compaction of these honeycomb
147 structures appears to be regulated by cholesterol. Through molecular dynamics simulations,
148 her team demonstrated that VDAC has a particular affinity for cholesterol and
149 phosphatidylethanolamine, both of which play a crucial role in the formation and stability of
150 these specific structures. Furthermore, she highlighted that deviations from the normal lipid
151 composition can significantly disrupt these native-like assemblies, underscoring the critical
152 role of lipid environments in VDAC organization. In conclusion, Lucie Bergdoll emphasized the
153 physiological importance of lipid heterogeneity and how changes in membrane composition,
154 whether due to membrane contact sites or pathological conditions, profoundly affect VDAC
155 behavior. This work sheds new light on the dynamic interplay between lipid environments and
156 mitochondrial function.

157 The selected speaker was Dr. Eleonora Centonze from the Department of Biomedical Sciences
158 at the University of Lausanne, Switzerland. She convincingly demonstrated that fluorescence
159 measurements can effectively probe protonation-driven conformational changes in the B-turn
160 domain of the acid-sensing ion channel ASIC1a. ASICs are voltage-independent, Na⁺-selective
161 channels activated by extracellular acidification, which results in transient inward currents
162 before the channel transitions to a non-conducting, desensitized state. This channel is highly
163 expressed in the central nervous system. Dr. Eleonora Centonze presented her recent findings
164 on the role of amino acid residues within the β -turn of hASIC1a during activation, using
165 voltage-clamp fluorometry. She particularly illustrated how this region, connecting the palm
166 and thumb domains, interacts with the transmembrane domain TM1 and influences channel
167 gating. Her work highlighted that investigating activity-dependent conformational changes
168 provides valuable insights into how protonation regulates ASIC activity, thereby deepening
169 our understanding of these channels.

170 Collectively, the symposium showcased the importance of a multidisciplinary approach of ion
171 channel research, enmeshing the intricate threads of protein conformation, lipid regulation,
172 protein assemblage in ion channel modulation and functions. These presentations powerfully
173 highlighted the crucial role of the ion channel environment, especially the composition of lipid
174 membranes, as highly valuable therapeutic targets. Moreover, such complementary
175 approaches are able to unveil non-ionotropic function of ion channels. They offer a hopeful
176 perspective for leveraging new, actionable insights in both preventive medicine and
177 therapeutic innovation.

178

179 **Symposium 2**

180 **Ion channels and cancer (organized by Loïc Lemonnier, Laboratoire de Physiologie Cellulaire,**
181 **Université de Lille, INSERM U1003, Villeneuve d'Ascq, France).**

182 While the role of ion channels in physiology and pathologies has been extensively documented
183 since their discovery, it is only recently that their involvement in cancer has been proposed.
184 Indeed, alterations in ion channel expression and function have been associated with all the
185 hallmarks of cancer, and extensive research is currently ongoing in order to propose
186 innovative treatments targeting ion channels to improve cancer patients care. The goal of this
187 session was thus to highlight recent advances on this topic, while raising general awareness
188 about this issue. This session was specifically supported by “La Ligue contre le cancer and
189 Cancéropôle Grand Sud-Ouest”.

190 The first speaker of the session was Prof. Barbara Ehrlich (Yale School of Medicine, CT, USA),
191 who presented a talk entitled “From Basic Science to Clinical Trials: Lessons from
192 Chemotherapy”. It is well-known that platinum-based chemotherapeutic agents used to treat
193 cancer can lead to peripheral neuropathies due to their neurotoxic effects. These effects are
194 experienced to some degree by a vast majority of patients, and they can induce a pain so
195 intense that the treatment has to be stopped. Prof. Ehrlich has shown that calcium signaling
196 plays an important role in this process, and that the IP3 receptor (IP3R) and Neuronal Calcium
197 Sensor 1 (NCS1) are involved. She has indeed shown that NCS1 can directly bind the IP3R
198 located in the endoplasmic reticulum (ER) membrane, and increase its activity. This interaction
199 is associated with an increase in dendritic complexity, and the use of mice KO for Ncs1 shows
200 that the side effects of paclitaxel require NCS1 presence. Moreover, chronic treatment with
201 paclitaxel decreases NCS1 expression, and lowers ER calcium content. This long-term effect
202 results from a direct activation of NCS1 by paclitaxel, leading to IP3R opening, ER calcium
203 stores depletion, and the activation of calpain that will degrade many proteins (including
204 NCS1) and induce neuronal damage. Finally, she has shown that lithium, by decreasing the
205 NCS1-induced calcium surge observed during a treatment with paclitaxel, can represent a
206 good tool to decrease the neurotoxicity of this drug while maintaining its anti-tumor efficacy.
207 The second speaker was Prof. Rainer Schindl (Medical University Graz, Austria), who
208 presented a talk entitled “Structural analysis of store-operated activation and
209 pathophysiological STIM1 mutants”. Store-operated calcium channels (SOCs) represent the
210 main calcium entry pathway in non-excitabile cells. SOCs are known to play a critical role in the
211 activation of immune cells, including T cells, in response to the formation of an immunological
212 synapse with antigen presenting cells or pathogens. SOCs activation results from the depletion
213 of ER calcium stores, detected by Stim1, an ER calcium sensor. Following ER depletion, Stim1
214 will form multimeric structures, go near the plasma membrane, and directly bind Orai
215 channels, the main molecular component of SOCs. Several Orai/Stim mutations have been
216 associated with T cells loss of function. Using molecular dynamics (MD) simulations, the team
217 of Prof. Schindl has shown that ER calcium stores depletion induces the unfolding of two EF
218 hand helices ($\alpha 2$ and $\alpha 3$) in Stim1. Using a similar approach, they predicted that Stim1
219 multimerization would require $\alpha 7$ and $\alpha 9$ helices from the SAM (Sterile Alpha Motif) domain.
220 This prediction was experimentally confirmed using Stim1 mutants for these two regions, the
221 mutants exhibiting an inability to form multimers, and inducing a decrease in SOC activity.
222 Finally, they presented evidence that mutations on residue H72 observed in cancer and
223 tubular aggregate myopathy patients lead to constitutive Stim1 activation, as predicted by MD

224 simulations. These results thus shed new light on the molecular mechanisms controlling SOC
225 activity.

226 The third speaker was Dr. Sébastien Roger (University of Tours, France), who presented a talk
227 entitled “Role of the P2X4 receptor in the fate of acidic compartments under metabolic
228 stress”. Dr. Roger first reminded us that tumor microenvironment favors the selection of
229 aggressive cancer cells, and that it contains an elevated concentration of ATP able to open P2X
230 ionotropic receptors. His team has shown that P2X4 is overexpressed in cancer cells, and that
231 it is mainly expressed in acidic compartments/lysosomes. P2X4 controls their fusion to: i)
232 autophagosomes thus promoting autophagy, fulfilling energy demands and allowing cancer
233 cell survival under metabolic stress conditions; ii) plasma membrane, promoting the release
234 of proteases, matrix degradation and invasiveness. P2X4 also controls the extracellular release
235 of small extracellular vesicles promoting the pro-invasive properties of cancer cells. In
236 conclusion, Dr. Sébastien Roger has shown that P2X4 not only controls the fate of intracellular
237 acidic compartments and mediates the hallmarks of cancer in response to metabolic stress,
238 but also modulates autophagy, invasion and cell-cell communication, making this receptor a
239 potential target for anticancer therapy.

240 The last presentation of the session was given by a PhD student, Mathilde Fourgeaud
241 (University Picardie Jules Verne, France). Her presentation was entitled “Impact of TRPM7
242 channel on pancreatic stellate cell activation induced by cadmium exposure”. Her work is done
243 in the context of pancreatic ductal adenocarcinoma (PDAC), a highly aggressive cancer with a
244 very low survival rate. Her host lab has previously shown that cadmium, a pollutant found in
245 high concentration in the urine of the French population, induces in PDAC cells an increase in
246 TRPM7 channel expression, and an increase in their invasion and migration properties. During
247 her PhD, Mathilde Fourgeaud has shown that cadmium elicits similar effects in pancreatic
248 stellate cells, leading to their activation via an increase in TRPM7 expression and activity. The
249 activation of stellate cells is known to stimulate PDAC cells aggressive behavior, and she shows
250 here that cadmium can represent a previously unknown trigger for this activation. Her work
251 therefore points to the importance of a better regulation of cadmium concentrations in food,
252 soils, water and air.

253

254 **Symposium 3**

255 **Channelopathies at preclinical - modeling channelopathies (organized by Adèle Faucherre,**
256 **Institut de Génomique Fonctionnelle, CNRS UMR 5203, Inserm U1191, Université de**
257 **Montpellier, Montpellier, France)**

258 Recent efforts in human genetics have greatly contributed to identify numerous pathological
259 variants in ion channel genes. Almost, if not all ion channel genes harbor mutations that are
260 responsible for a variety of severe, early-onset diseases, called channelopathies. Clinical
261 manifestations of channelopathies are diverse, reflecting the wide range of physiological
262 processes that ion channels control. Given the complexity and variability of these disorders,
263 which can affect a wide range of organs or tissues, further research into channelopathies is
264 essential to better understand the subtleties of ion channel function and to develop innovative
265 treatments that can improve outcomes for patients with these challenging conditions. To gain
266 a better understanding of pathogenic mechanisms, it is necessary to develop and characterize
267 models of human channelopathies, using cellular and animal models.

268 This symposium presented recent advances validating and exploiting these models, starting
269 with Prof. Dominique Glauser (University of Fribourg, Switzerland), who presented a talk
270 entitled "Computer-assisted behavioral phenotyping in *C. Elegans* as a tool to study channel
271 function and dysfunction". Due to a number of advantages such as rapid growth, powerful
272 genetic tools, a transparent body and compact nervous system, as well as the conserved
273 homology of genes encoding ion channels, the nematode *C. elegans* represents a
274 complementary model for the study of complex phenomena involving ion channels. Prof.
275 Glauser presented studies on the molecular mechanisms controlling thermo-nociceptive
276 behavior and nociceptive plasticity. Using a computer-assisted thermal avoidance analysis
277 pipeline to screen for behavioral defects, his lab has identified mutants in genes orthologous
278 to human pain-related genes, including voltage-gated, ligand-gated ion channels. This led to
279 general perspectives for generating worm-based models to study channel function and
280 dysfunction.

281 Next, Prof. Carol Ann Remme (Amsterdam University Medical Center, The Netherlands)
282 presented her work on "SCN5A channelopathy: arrhythmia, cardiomyopathy, and beyond the
283 cardiomyocyte". As it is known that the sodium channel *SCN5A/Nav1.5* plays a role in cardiac
284 channelopathies, she emphasized the pleiotropic role of the Nav1.5 channel, whether directly
285 or indirectly linked to its Na⁺ channel function, and stressed the non-channel dysfunctions of
286 Nav1.5. She showed that Nav1.5 channel interacts with proteins in the lateral membrane and
287 in the intercalary disc region. She also exposed that microtubule dynamics can affect Nav1.5
288 expression and current, and be linked to Arrhythmogenic Right Ventricular Cardiomyopathy.
289 Finally, she showed that Nav1.5 was also present in non-cardiomyocytes cells such as
290 intracardiac neurons where it could be involved in pro-arrhythmic mechanism.

291 The third speaker, Dr. Nadine Ortner (Institute of Pharmacy - University of Innsbruck, Austria),
292 gave a lecture on "Cav1.3 variants: from molecular mechanisms to therapeutic approaches".
293 The L-type voltage-gated Ca²⁺ channel Cav1.3 (*CACNA1D* gene) is a high-risk gene for
294 neurodevelopmental disorders with or without endocrine features. After mentioning the
295 functional and clinical variability of *CACNA1D* variants, she focused her presentation on the
296 characterization of a knock-in mouse model carrying the A749G variant. This included general
297 phenotype such as developmental delay, study of the endocrine system, and assessment of
298 cellular excitability or behavioral analysis. This mouse model allowed her lab to successfully
299 evaluate potential therapeutic strategies *in vivo*.

300 Finally, as a selected speaker, Dr. Shi-Bing Yang (Academia Sinica, Taiwan) gave a presentation
301 entitled "Beyond Membrane Excitability: Gain-of-function KATP Channel Mutant Causes
302 Permanent Neonatal Diabetes via Suppressing Beta Cell Proliferation". Using a genetic
303 approach for mimicking *de novo* mutations, he developed a model of Neonatal Diabetes
304 displaying a conditional mutation of ATP-sensitive potassium channel Kir6.2/*KCNJ11*. Using
305 this model, he showed that KATP channels were involved in β-cell mass and insulin secretion
306 regulation.

307

308 **Symposium 4**

309 **Channelopathies at molecular - from structure to pharmacology (organized by Philippe Lory**
310 **Institut de Génomique Fonctionnelle, CNRS UMR 5203, Inserm U1191, Université de**
311 **Montpellier, Montpellier, France).**

312 The fourth symposium highlighted findings and approaches developed to tackle the molecular
313 targeting and therapeutic specificities of channelopathies, starting with Dr. Barbara Ribeiro
314 (Institut du Thorax, Université de Nantes, France) with a talk entitled: “Functional
315 Characterization of *KCNH2* genetic variants, encoding hERG potassium channel, as a clinically-
316 relevant information for type-2 LQTS syndrome”. Long QT syndrome type 2 (LQTS2) is a
317 potentially fatal cardiac arrhythmia disorder, often resulting from rare loss-of-function
318 variations in the *KCNH2* gene, encoding the hERG cardiac channel. Dr. Barbara Ribeiro
319 presented a study based on a large-scale multi-parametric evaluation of the 300 *KCNH2*/hERG
320 variants identified within the French CARDIOGEN network. High-throughput electrophysiology
321 (HTE) using an automated patch-clamp system allowed fast analysis of this large number of
322 *KCNH2* variants, improving the statistical value of the obtained results. This approach allowed
323 to reclassify 179 ‘variants of uncertain significance’ (VUS), for an optimal stratification of the
324 rhythmic risk for the related patients. Such a HTE approach is critically needed, as more than
325 3000 variants of the *KCNH2* gene have been identified to date (ClinVar database), and their
326 potential pathogenicity remains unknown for most of them.

327 Next, Prof. Henry Colecraft (University of Columbia, New York, USA) presented his talk on
328 “Hacking the Ubiquitin code to control ion channel expression for therapy”. Small molecules
329 would be ideally suited as drugs for selectively inhibiting or activating ion channels in the
330 treatment of channelopathies. However, such therapeutics are still missing. Prof. Henry
331 Colecraft identified that dozens of human diseases are due to either too little or too much
332 functional expression of particular channel proteins. The ubiquitin-proteasomal system may
333 hold the solution to all such diseases to selectively manage increase or decrease of ion channel
334 expression. Prof. Colecraft lab has developed protein engineering approaches to target
335 protein stabilization or destabilization to correct diverse ion channel-related diseases such as
336 cardiac arrhythmias, cystic fibrosis, epilepsy, and pain. One good example is the recruitment
337 of the endogenous NEDD4-2 E3 ubiquitin ligase with designed nanobodies to generate novel
338 genetically-encoded ion channel inhibitors.

339 The third speaker of this symposium was Prof. Jean-François Desaphy (University of Bari, Italy)
340 presenting “Mutation-driven precision medicine in non-dystrophic myotonias”. Non-
341 dystrophic myotonias are skeletal muscle diseases due to mutations in the sodium channel
342 Nav1.4 or the chloride channel ClC-1, causing myofibers hyper-excitability. Nav blockers such
343 as mexiletine have been empirically used for decades in myotonia, regardless the culprit gene,
344 because they reduce action potential firing in myofibers. Randomized clinical trials confirmed
345 effectiveness in myotonic patients. However, several patients complain of poor tolerability or
346 unsatisfactory response to mexiletine. Some of these patients, carrying variants displaying a
347 negative shift of fast voltage-dependent inactivation, were successfully treated with
348 flecainide. This work shows the importance of having *in vitro* pharmacological studies that can
349 be translated to humans, supporting the effectiveness of precision medicine in myotonic
350 individuals.

351 Finally, the PhD student Lamia Goual (PhyMedExp, Université Montpellier, France) who was
352 the selected speaker of this session, gave a presentation entitled “Modeling the Neurocardiac
353 junction in Long QT Syndrome type-2”. LQTS2 (described above) can be considered as a
354 ‘neuro-cardiac’ syndrome as patients are experiencing cardiac QT prolongation and epilepsy
355 phenotype, which may lead to SUDEP (Sudden Unexpected Death in Epilepsy). Lamia Goual

356 has developed from such a LQTS2 patient, iPSC-derived cardiomyocytes and neurons to model
357 the neurocardiac axis. Using microfluidic compartmentalized chambers, she established a
358 network of differentiated hiPSC-derived ventricular cardiomyocytes with sympathetic
359 neurons to mimic the neurocardiac innervation. This innovative methodology should help
360 decipher the dysfunctions underlying the LQT2 syndrome.

361

362 **Symposium 5**

363 **Glutamate receptors: trafficking, turnover, plasticity, agonists (organized by Vincent Seutin,** 364 **Laboratory of Neurophysiology, GIGA Neurosciences, University of Liège, Belgium).**

365 Given their paramount importance, glutamate receptors are abundantly studied in
366 Neuroscience. In this symposium, we wanted to cover some outstanding questions, such as
367 the nature of the co-agonist at NMDA receptors, the regulation of its local abundance, and
368 the most important stoichiometries of NMDA and AMPA receptors in given brain areas.

369 Dr. Aude Panatier (Neurocentre Magendie, INSERM U1215, Université de Bordeaux, France)
370 started this session by showcasing the influence of EphB3 receptors on the physiology of
371 glutamatergic synapses. The activation of classical NMDA receptors (NMDARs) requires the
372 binding of glutamate and of a co-agonist. D-serine released from astrocytes is acting as such
373 a co-agonist at several central synapses. In the hippocampus, while D-serine is the co-agonist
374 of synaptic NMDARs, glycine is the one at extra-synaptic sites. Interestingly, it has been shown
375 in astrocytic cultures that astrocytic EphB3 receptors play a role in the synthesis and release
376 of D-serine. However, whether it could impact synaptic NMDAR activity in a more
377 physiological setting was unknown. Panatier's team first established that the stimulation of
378 EphB receptors by exogenous ephrinB3 leads to an increase of D-serine availability at CA3-CA1
379 synapses, inducing an increase of NMDAR activity. Importantly, the inhibition of endogenous
380 EphB3 receptors impaired NMDAR activity, strongly suggesting an endogenous tone at this
381 receptor. These effects depend on astrocytes as EphB3 receptor activation by exogenous
382 ephrinB3 had no impact on NMDAR activity under conditions where calcium dynamics was
383 inhibited specifically in astrocytes. Finally, the knockdown of EphB3 receptors specifically in
384 astrocytes led to impairments in both LTP and novel object recognition memory. Both defects
385 were rescued by exogenous D-serine. Thus, astrocytic EphB3 receptors play a key role in
386 synaptic NMDAR function and memory.

387 Prof. Mark Farrant (University College London, UK) described recent work carried out by his
388 team in the field of AMPA receptors (AMPA receptors) that play a crucial role in fast excitatory
389 synaptic signalling in the central nervous system. These receptors are encoded by the genes
390 *GRIA1-4*, and the four AMPAR subunit proteins (GluA1-4) can assemble as homo- or
391 heterotetramers, creating a variety of receptor subtypes. Of the AMPAR subunits, GluA2 is
392 particularly significant, because its presence determines key biophysical properties of the
393 receptors. Specifically, the inclusion of GluA2 reduces the channel's conductance and
394 transforms the receptor from being calcium-permeable to calcium-impermeable. Mark
395 showed how AMPAR diversity is further extended by co-assembly with various auxiliary
396 subunits such as the transmembrane AMPAR regulatory proteins (TARPs). Ligands of TARPs
397 are able to profoundly alter channel function. For example, one negative modulator of
398 TARP γ 8 was able to affect single channel conductance and kinetics of channel
399 desensitization. A large part of his talk was devoted to the study of *GRIA2* variants that are

400 linked to neurodevelopmental disorders. Pathogenic variants of *GRIA1-4* have been described
401 in patients with developmental delay, intellectual disability, autism spectrum disorder, and
402 seizures. Typically, *GRIA2* variants cause AMPAR loss of function. However, Farrant's team
403 discovered a new heterozygous de novo mutation (A643V) that exhibited a clear gain of
404 function, with slowed deactivation, markedly reduced desensitization, and increased
405 glutamate sensitivity. Perampanel, an anticonvulsant that specifically targets AMPARs, was
406 able to fully block GluA2 A643V currents in the presence of a TARP. The subsequent
407 introduction of perampanel to the patient's treatment regimen was associated with a marked
408 reduction in seizure burden and clear developmental gains. This was a very nice example of *in*
409 *vitro* therapeutic testing of a drug.

410 Dr. Nelson Rebola (Institut Du Cerveau, Paris Brain Institute ICM, Paris, France) reminded us
411 that the density as well as subunit composition of synaptic NMDA receptors (NMDARs) vary
412 considerably between synapses and between neurons. Despite the well-documented
413 heterogeneity of NMDARs, the functional relevance of such diversity is poorly known. In the
414 past, the functional relevance of NMDAR diversity was mostly considered in the context of
415 neuronal development and long-term synaptic plasticity. However, it has been recently found
416 that everyday dendritic computations are strongly influenced by the synaptic density and
417 biophysical properties of NMDARs. Dr Rebola's team decided to investigate this question in
418 cortical interneurons (INs). They found that the density of synaptic NMDARs is quite different
419 between somatostatin (SST) and parvalbumin (PV)- interneurons (INs). Experimental and
420 theoretical analyses indicate that such differences in the levels of synaptic NMDAR have a
421 significant impact in dendritic integration properties of cortical INs. Using two-photon
422 glutamate uncaging, they observed that SST-INs present NMDA receptor-dependent
423 supralinear dendritic integration (i.e.: the sum of synaptic potentials generated by close by
424 synapses is larger than their arithmetic sum), while PV-INs express distance-dependent
425 sublinear synaptic integration. Model simulations suggested that the distinct dendritic
426 integration properties affect the temporal activity profile of these two IN populations. When
427 digging into the possible molecular mechanisms of the difference, Dr Rebola's team found that
428 SST-INs are equipped with the atypical glycine-binding NMDAR subunit, GluN3A, which forms
429 atypical excitatory GluN1/GluN3A receptors. Dr Rebola concluded by stating that the diversity
430 of NMDAR-dependent signalling is crucial for information processing within cortical networks.
431 The final speaker, Sofian Ringlet (PhD student, Laboratory of Neurophysiology, GIGA
432 Neurosciences, University of Liège, Belgium) addressed the molecular composition and co-
433 agonist nature of NMDARs expressed in dopaminergic (DA) neurons located in the substantia
434 nigra. These neurons are crucial for the control of movement. This vital function is encoded
435 by the firing pattern of DA neurons which switches between spontaneous firing and bursts of
436 action potentials. The latter produces an increase of DA release in targeted areas which is
437 associated with locomotion initiation. The impairment of this signal, which occurs during DA
438 neuron degeneration, leads to the motor symptoms of Parkinson's disease. Previous research
439 has shown that activation of the NMDARs by the simultaneous binding of glutamate and a co-
440 agonist is indispensable for the generation of this physiological cue. In these neurons, the
441 identity of the endogenous coagonist responsible for the production of bursting activity
442 remained unknown. Sofian made use of enzymes that specifically degrade either glycine or D-
443 serine (previously developed by Dr Loredano Pollegioni (University of Varese, Italy). Using

444 whole-cell patch-clamp recordings in brain slices from wild-type Wistar rats (4-7 weeks old),
445 he found that D-serine and glycine bind to synaptic and extrasynaptic NMDARs, respectively,
446 even though both high resolution imaging and pharmacological experiments revealed that
447 both NMDAR populations are composed of the same subunits (GluN1-GluN2B-D
448 triheteromers). Interestingly, burst generation required the same co-agonist as the one
449 necessary for extrasynaptic NMDARs (i.e. glycine). In addition, the generation and general
450 pattern of bursts were not affected by the specific blockade of synaptic NMDARs. Thus, both
451 glutamate acting on extrasynaptic NMDA receptors (probably during intense synaptic activity)
452 and glycine are needed for bursting in DA neurons.

453

454 **Poster presentations**

455 The two poster sessions highlighted the diverse and cutting-edge research on ion channels,
456 their physiological roles, and their implications in diseases and therapeutics. The structural,
457 functional, and pharmacological characterization of ion channels across different systems,
458 spanning cardiac conduction, neural signalling, cancer and sensory mechanisms have been the
459 key themes of the posters. Research presented ranged from channelopathies, like KCNQ1
460 mutations enhancing WNT/ β -catenin signalling and CACNA1D variants affecting calcium
461 channel gating, to advances in therapeutic approaches such as peptide blockers for Cav1.2
462 and monoclonal antibodies targeting TRPV6 in cancer. Novel findings on mechanisms
463 underlying sinus node dysfunction, Nav1.4 mutations in paramyotonia congenita and ASIC1A
464 gating regulation have been proposed. Moreover, emerging technologies, such as organ-on-
465 chip models for neuro-cardiac junctions and graphene nanodevices for ion channel detection,
466 demonstrating innovation in experimental approaches were also presented. Poster sessions
467 also delved into ecological perspectives, such as insecticide effects on neuronal receptors and
468 evolutionary insights from honeybee CaV4 channels. These vibrant sessions provided a
469 comprehensive view of ion channel research, bridging molecular mechanisms, translational
470 applications, and novel methodological advancements to address critical questions in
471 physiology and disease.

472

473 **Conclusion**

474 This edition, as all the previous ones, has been characterized by scientific presentations and
475 discussions of outstanding quality. All participants appreciated the possibility to discuss of
476 science out of the framework of the 'imposed' symposia, during the coffee break and at lunch
477 surrounded by the extraordinary atmosphere of the south of France at Mediterranean seaside
478 or after dinner at the sunset.

479

480 **Acknowledgments**

481 We thank all the sponsors who helped us making this congress possible:

482 Cancéropôle Grand Sud-Ouest, French Society for Cell Biology, INM-Institute for
483 neurosciences Montpellier, La Ligue Contre le Cancer, Labex ICST-Ion channels Science and
484 Therapeutics, LabUM EpiGenMed, MappingLab, Micromecanique SAS & Electrophysiologie.fr,
485 Nanion, Scientifica, SCOP Pro, Sophion Bioscience, Taylor & Francis Group, Université de
486 Montpellier, WPI-World Precision Instruments.

487 We are grateful to Dr. Caroline Strube and Dr. Arnaud Monteil, who take care to preserve for
488 more than twenty years the soul of this meeting which is above all a convivial moment of
489 quality scientific exchange.

490

491 **Author Disclosure Statement**

492 The authors declare no conflict of interest. Informed consent was obtained from all the
493 participants involved in this study.

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Participants during cocktail-dinner party

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