

# ***Application for an International Research Network (IRN)***

## **France-Taiwan Initiative for Ion Channels and Therapeutics**

### **1) PRESENTATION**

#### **a) Name and acronym of the project**

France-Taiwan Initiative for iON channels and TherapeutICs (IONIC).

#### **b) Names of the French and foreign coordinators, their laboratories, departments and institutions with addresses (postal and e-mail)**

- Dr. Emmanuel Deval, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), UMR 7275 CNRS/University Côte d'Azur (UCA), team "Ion channels and Pain", 660 route des Lucioles, 06560 Valbonne, France ([deval@ipmc.cnrs.fr](mailto:deval@ipmc.cnrs.fr)).

- Dr. Cheng-Chang Lien, Institute of Neuroscience, National Yang-Ming University (NYMU), 155, section 2, Linong street, Taipei 112, Taiwan ([cclien@ym.edu.tw](mailto:cclien@ym.edu.tw)).

- Dr. Chih-Cheng Chen, Institute of Biomedical Sciences, Academia Sinica, 128, section 2, academia road, Taipei 115, Taiwan ([chih@ibms.sinica.edu.tw](mailto:chih@ibms.sinica.edu.tw)).

#### **c) Names of the other participants, their laboratories, departments and institutions with addresses (French and foreign)**

- Dr. Eric Honoré, IPMC, UMR 7275 CNRS/UCA, team "Molecular and Integrative Mechanobiology", 660 route des Lucioles, 06560 Valbonne, France ([honore@ipmc.cnrs.fr](mailto:honore@ipmc.cnrs.fr)).

- Dr. Florian Lesage, IPMC, UMR 7275 CNRS/UCA, team "Molecular physiology and Pathophysiology of Ion Channels", 660 route des Lucioles, 06560 Valbonne, France ([lesage@ipmc.cnrs.fr](mailto:lesage@ipmc.cnrs.fr)).

- Dr Eric Lingueglia, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), UMR 7275 CNRS/University Côte d'Azur (UCA), team "Ion channels and Pain", 660 route des Lucioles, 06560 Valbonne, France ([lingueglia@ipmc.cnrs.fr](mailto:lingueglia@ipmc.cnrs.fr)).

- Dr. Emmanuel Bourinet, Institut de Génomique Fonctionnelle (IGF), UMR 5203 CNRS/INSERM/Université de Montpellier, 141, rue de la Cardonille 34094 Montpellier cedex 5 ([emmanuel.bourinet@igf.cnrs.fr](mailto:emmanuel.bourinet@igf.cnrs.fr)).

- Dr. Shi-Bing Yang, Institute of Biomedical Sciences, Academia Sinica, 128 section 2, academia road, Taipei 115, Taiwan ([sbyang@ibms.sinica.edu.tw](mailto:sbyang@ibms.sinica.edu.tw)).

- Dr. Jr-Kai Sky Yu, Institute of Cellular and Organismic Biology, Academia Sinica, 128 section 2, academia road, Taipei 115, Taiwan ([jkyu@gate.sinica.edu.tw](mailto:jkyu@gate.sinica.edu.tw)).

- Dr. Chien-Chang Chen, Institute of Biomedical Sciences, Academia Sinica, 128 section 2, academia road, Taipei 115 ([ccchen@ibms.sinica.edu.tw](mailto:ccchen@ibms.sinica.edu.tw)).

## 2) ABSTRACT IN FRENCH AND IN ENGLISH

Résumé : Les canaux ioniques sont des protéines membranaires clés qui contrôlent le flux d'ions tels que le sodium, le potassium, le calcium ou le chlorure dans les cellules vivantes. Ils sont nécessaires à plusieurs processus physiologiques et de nombreux dysfonctionnements des canaux ioniques sont associés à des états pathologiques tels que l'épilepsie, l'hypersensibilité ou l'insensibilité à la douleur, les arythmies cardiaques ou encore les troubles cognitifs. Les canaux ioniques constituent ainsi une classe importante de cibles thérapeutiques et les médicaments modulant leur activité ont connu un grand succès, générant plus de 12 milliards d'euros de ventes par an au niveau mondial. Malgré cela, de nombreuses maladies restent mal traitées et il y a encore un réel besoin de mieux comprendre la complexité et la plasticité des fonctions des canaux ioniques, y compris l'étude de leur régulation et l'identification de nouveaux canaux à potentiel thérapeutique.

Ce projet vise à développer un réseau international de laboratoires de recherche Franco-Taïwanais afin de constituer un consortium de premier plan dans le domaine de la science et de la thérapeutique des canaux ioniques, qui sera en mesure de solliciter des subventions internationales. En partageant leurs expertises, leurs outils et leurs méthodes, les équipes participantes adopteront une approche intégrée et systématique pour identifier et valider les protéines et les modulateurs des canaux ioniques en tant que nouvelles cibles et/ou biomarqueurs de médicaments appropriés pour les interventions thérapeutiques et diagnostiques. Ce réseau produira des résultats novateurs dans le domaine de la recherche fondamentale et de la recherche translationnelle, qui déboucheront sur des partenariats renforcés avec des entreprises privées, ainsi que sur une formation attrayante. Les synergies créées par ce programme renforceront la visibilité internationale des équipes et de leurs instituts d'accueil, ce qui accroîtra l'attrait pour les étudiants et les chercheurs de haut niveau.

Abstract: Ion channels are key membrane proteins that control the flow of ions such as sodium, potassium, calcium or chloride, into and out of living cells. They are necessary for several physiological processes and numerous ion channel dysfunctions are associated to disease states, including epilepsy, hypersensitivity or insensitivity to pain, cardiac arrhythmia and cognitive dysfunctions. Ion channels thus constitute a prominent class of therapeutic targets and drugs modulating their activity have been very successful, generating more than €12 billion in global sales per annum. Despite this, many diseases remain poorly treated and there is still a real need to better understand the complexity and plasticity of ion channel functions including study of their regulations and identification of new channels with therapeutic potential.

The proposed project aims at developing an international France/Taiwan research network of laboratories to build a leading consortium on Ion Channel Science and Therapeutics, which will be able to apply for international grant calls. By sharing expertise, tools and methods, participating teams will undertake an integrative and systematic approach to identify and validate ion channel proteins and modulators as novel drug targets and/or biomarkers appropriate for therapeutic and diagnostic interventions. This network will generate innovative outputs in basic and translational research leading to enhanced partnerships with private companies, as well as attractive training. The synergies created through this program will reinforce the international visibility of the individual teams and their hosting institutes, enhancing attractiveness for high profile students and researchers.

### 3) HISTORICAL CONTEXT OF THE COLLABORATION

This project was initiated upon common scientific interests in the field of ion channel research. In 2017, Dr. Eric Honoré went to Taipei to visit NYMU and Academia Sinica. Dr Cheng-Chang Lien then visited IPMC and attended the 28<sup>th</sup> Ion Channel Meeting in Sète, France. In 2018, we obtained a grant from Campus France (PHC ORCHID n°40858VJ), allowing us to organize different scientific events:

- In September 2018, 8 Taiwanese research scientists (from 8 research teams belonging to NYMU, National Taiwan University (NTU), Academia Sinica in Taipei, and Kaohsiung Medical University in Kaohsiung) attended the 29<sup>th</sup> Ion Channel Meeting in Sète, France (September 9-12<sup>th</sup>). A special session of the meeting was dedicated to Ion Channel Research in Taiwan, including biophysics and physiology as well as pharmacology. This 2018 edition was an opportunity for the organizing committee to broaden the international scope of this Ion Channel Meeting by inviting a delegation of Taiwanese researchers. It was also the opportunity to have fruitful scientific exchanges and develop links between the French and Taiwanese “Ion Channel” community.

- In December 2018, 6 French research scientists (from 4 research teams belonging to IPMC-CNRS-UCA and INSERM-University of Nantes) went to Taiwan and visited Academia Sinica, NYMU and NTU Medical College. This visit provided the opportunity to organize a bilateral symposium where French and Taiwanese researchers presented their work on ion channels (ASIC, Cav, Nav, Kir, Kv, K2P, PIEZO, P2X and TRP channels) and shared fruitful scientific discussions. Mr. Benoit Lepine (in charge of Scientific and Academic Cooperation in Taipei for the French Ministry of foreign affairs) also attended the symposium and presented the different collaboration opportunities between the two countries. French researchers also met with Taiwanese students at NYMU and Dr. Amanda Patel (IPMC) provided an overview of the CNRS, UCA, as well as available graduate programs.

### 4) DESCRIPTION OF THE SCIENTIFIC PROJECT

Ion channels are key membrane proteins that control the flow of ions such as sodium, potassium, calcium and chloride, into and out of living cells. They are necessary for several physiological processes including hormone secretion, muscle contraction, nerve impulse, cardiovascular function, and are involved in sensory and pain perception. Numerous ion channel dysfunctions or dysregulations are associated with pathophysiological conditions leading to, for instance, epilepsy, hypersensitivity or insensitivity to pain, cardiac arrhythmia or cognitive dysfunctions. The pore-forming subunits of ion channels thus constitute a prominent class of therapeutic targets. Indeed, drugs modulating their activity have been very successful and generate more than €12 billion in global sales per annum. Despite this, many diseases remain poorly treated and there is a real need to better understand the complexity and plasticity of ion channels including their regulations, association with auxiliary subunits, addressing to specific membrane sub-domains, intracellular trafficking, membrane recycling, post-translational modifications and epigenetic regulations, together with the identification of new ion channels with therapeutic potential.

The proposed project aims at developing an international France/Taiwan research network of laboratories focusing on Ion Channel Science and Therapeutics. By sharing expertise, tools and methods, participating teams will undertake an integrative and systematic approach to identify and validate ion channel proteins and modulators as novel drug targets and/or biomarkers appropriate

for therapeutic and diagnostic interventions. This network will generate innovative outputs in basic and translational research leading to enhanced partnerships with private companies, as well as attractive training. The synergies created through this program will reinforce the international visibility of the individual teams and their hosting institutes, enhancing attractiveness for high profile students and researchers.

The research program includes three main axes:

- Identification of novel targets of therapeutic interest, ion channels and their modulators.
- Validation of targets at the molecular, cellular, organ and animal levels.
- Development of new methods for studying ion channels.

This project involves, for the French part, 3 teams from the “Institut de Pharmacologie Moléculaire et Cellulaire” (IPMC, UMR 7275 CNRS/Université Côte d’Azur), which is a renowned center for ion channel research. The University Côte d’Azur (UCA) is one of the few top multidisciplinary universities in France (Index JEDI). Moreover, this project will be in direct link with the Laboratory of Excellence (LabEx) “Ion Channel Science and Therapeutics” coordinated by Dr. Florian Lesage (IPMC-UMR 7275, [lesage@ipmc.cnrs.fr](mailto:lesage@ipmc.cnrs.fr)). The IPMC teams involved in the IRN application are:

1. Dr. Eric Honore’s team (member of the LabEx ICST), which is focused on mechano-sensitive ion channels;
2. Dr. Florian Lesage’s team (director of the LabEx ICST), which studies background  $K_{2P}$  channels;
3. Drs. Eric Lingueglia and Emmanuel Deval’s team (member of the LabEx ICST), which is studying the molecular physiology and pharmacology of ASIC channels and their role in pain.

In addition, one team from IGF (CNRS, Montpellier) is also partner of this network:

4. Dr. Emmanuel Bourinet’s team (IGF, Montpellier, member of the LabEx ICST), which is focusing on the role of ion channels in pain and somatosensory perception, with a special interest for voltage-gated calcium channels and mechanoreceptors.

Taiwanese partners are belonging to National Yang-Ming University (NYMU), and Academia Sinica in Taipei. Five research teams are involved in the IRN, including:

1. Dr. Cheng-Chang Lien’s team (Institute of Neuroscience, National Yang-Ming University), which is working on ASIC channels and GABA<sub>A</sub> receptors.
2. Dr. Chih-Cheng Chen’s team (Institute of Biomedical Sciences, Academia Sinica), which is focusing on the role of ASICs in the somatosensory system.
3. Dr. Shi-Bing Yang’s team (Institute of Biomedical Sciences, Academia Sinica), which is working on pH-sensitive  $K_{2P}$  channels.
4. Dr. Chien-Chang Chen (Institute of Biomedical Sciences, Academia Sinica) is working on the Role of Cav3.2 in cardiovascular system.
5. Dr. Jr-Kai Sky Yu’s team (Institute of Cellular and Organismic Biology, Academia Sinica), which is working on Marine Biology and evolution of development.

## 5) DESCRIBE THE INTEREST OF STRUCTURING THE SCIENTIFIC COMMUNITY AROUND THE CHOSEN THEME AND THE PERTINENCE OF THE CONSORTIUM

The main interests of structuring this France/Taiwan scientific community around ion channel research are to:

- Stimulate collaboration and scientific exchanges (including faculty sabbaticals) on particular ion channels and their pathophysiological contribution (shared interests on ASIC,  $K_{2P}$  and Cav3.2 channels, on pain, somatosensory perception and cardiac physiology).
- Identify novel ion channel modulators and develop a specific pharmacology with a special emphasis on traditional Taiwanese medicine and marine pharmacological reagents.
- Facilitate PhD student exchanges with the aim to enroll Taiwanese students in the French PhD programs or attract post-doctoral fellows.
- Give an international connection that can benefit to all the Labex ICST members.

## 6) DESCRIPTION OF THE ADDED VALUE OF THE INTERNATIONAL COOPERATION

This France/Taiwan research network is based on a common interest for ion channel research, the particular scientific know-how and tools developed by each of the teams of this consortium. The project could not be carried out at the national levels because teams within this network were selected due to the unique tools and expertise they have developed at their individual levels. For instance, Dr. Lesage cloned most of the members of the  $K_{2P}$  channel family and has developed original mouse strains (single, double and triple knockouts for different  $K_{2P}$  channels) that will be studied in collaboration. French researchers already visited the Academia Sinica Behavioral Center (Taiwan Mouse Clinic; <http://tmc.sinica.edu.tw/index.html>) managed by Dr. Chih-Cheng Chen, which allows phenotyping of genetically modified mouse strains (knockout, knockin...). Drs. Chih-Cheng Chen and Cheng-Chang Lien have engineered mouse strains for several ASIC channels, which could be used for spinal cord *in vivo* electrophysiological experiments developed by the team of Dr. Lingueglia and Dr. Deval (a MTA between NYMU and CNRS has already been signed for a particular mouse strain). Reciprocally, the pharmacological tools developed by the team of Drs Lingueglia and Deval would be of interest for the work done by Drs. Chi-Cheng Chen and Lien. Dr. Bourinet and Dr. Chien-Chang Chen are specialists of calcium channels in the field of pain and cardiac physiology. Another added value for the pharmacological aspect of the project will come from Dr. Jr-Kai Sky Yu, who is the chief of Marine Research Station at Academia Sinica, and who will play a key role in collecting unique marine animal venoms to possibly identify new original tools for ion channel studies in the consortium.

## 7) DESCRIPTION OF THE ACTIVITIES IN THE FRAMEWORK OF THE PROJECT AND PROVIDE A TIMETABLE

The main activities that will be carried out in this project are based on (i) scientific collaborations between French and Taiwanese research teams, (ii) annual meeting organization and (iii) student exchanges.

Scientific collaborations are already planned between the teams of Dr. Chih-Cheng Chen, Dr. Lien, and Drs. Deval and Lingueglia on the properties and the role of Acid-Sensing Ion Channels (ASICs) in pain and somatosensory perception, as well as between the teams of Dr. Lesage and Dr. Yang on pH-sensitive  $K_{2p}$  channels. As mentioned previously, collaborations on engineered mouse strains produced for several ion channels in the French or Taiwanese laboratories of the consortium will also be established. We also plan to initiate other collaborations paying a special attention to collaborations with Taiwanese colleagues working on traditional Chinese medicine. We will also take advantage of the Marine Research Station (Academia Sinica; <http://icob.sinica.edu.tw/mrs/>), which is part of the consortium, to obtain marine compounds. These compounds as well as those from traditional Chinese medicine will be screened on different ion channels taking advantage of IPMC's long lasting experience in identifying pharmacological modulators of ion channels. Screenings could also be performed when necessary using facilities available through the LabEx ICST. The aim is to identify novel compounds able to modulate ion channels with a therapeutical potential for the treatment of a broad range of diseases, including chronic pain, epilepsy and cardiac arrhythmias.

Another important point of this project will be to organize a bilateral annual meeting between French and Taiwanese researchers. These meetings will not only be the opportunity for researchers and PhD students to present their works to the community, but also to organize exchanges with Master and Graduate students, as well as visits of the Universities and laboratories. The first bilateral meeting will be organized in 2020 at IPMC and will be opened to the Labex ICST members (18 teams all over France) as well as to the whole scientific community of the University Côte d'Azur (UCA) to nurture new exchanges and collaborations. We will then alternate for the organization between Taiwan and France for the entire duration of the IRN.

Finally, this project will also provide travel grants for PhD students to carry out specific experiments in the French or Taiwanese laboratories of the consortium.

## 8) INVOLVEMENT OF STUDENTS AND/OR YOUNG RESEARCHERS IN THE PROJECT

This project will give a particular attention to PhD students and young researchers in order to promote exchanges between French and Taiwanese institutions:

- PhD students and post-docs will have the opportunity to present their works at the annual bilateral meetings organized alternatively in France and in Taiwan.
- Specific exchanges sessions will be organized during each annual bilateral meeting to allow Master and graduated students to discuss with French and Taiwanese researchers.

- Travel grants will be given to PhD students for exchanges between the different French or Taiwanese teams, allowing them to carry out specific experiments and learn new technical skills.

## 9) SCIENTIFIC QUALITY OF THE TEAMS

### Team Lingueglia/Deval:

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### Team Honoré:

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#### Team Lesage:

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#### Team Bourinet:

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#### PLANNED ANNUAL BUDGET AND FUNDING SOURCES

An annual budget of 15 k€ per year is anticipated, which includes organization costs and contribution to travels for researcher and PhD students attending the annual bilateral meetings (10k€/year), and travel grants for PhD students to perform specific experiments and learn new technical skills in French or Taiwanese labs (5k€/year).

#### 10) ETHICS

This project does not raise any specific ethical questions that are not covered by the individual team projects all covered by ethical accreditations.