We are seeking for a motivated PhD candidate to join our laboratory at the Cardiovascular Pathophysiology Group in the UAM Campus (Madrid, Spain). Our current research interests focus on Ion channels form signaling complexes or channelosomes, which are essential for optimal, fast and efficient signal transmission. Therefore, knowledge of the composition of these channelosomes is essential for the validation of new proteins that may constitute therapeutic targets, as well as for the design and synthesis of new chemical agents that may be useful drug candidates. The subproject 1 research group has demonstrated the existence of the Kv1.5 channelosome. The ultrafast and transient potassium outward currents (IKur and Ito, respectively) are mainly responsible for the atrial repolarization process and are generated after activation of the Kv1.5 and Kv4.3 channels, respectively. In the present project, we propose: a) the study of the interactions between KChIP2-Kv1.5 and Lgi3-4 and the Kv1.5 and Kv4.3 channels; b) the search for new interactors of both channelosomes; c) the search for new modulators and fluorescence biosensors for the study of protein interactions in the Kv1. 5 and Kv4.3 channelosomes as a source of new drugs for the treatment of atrial fibrillation (AF), the most common arrhythmia diagnosed in clinical practice; and d) voltage-sensitive fluorescent sensors. The combination of molecular design, organic synthesis, biophysics, electrophysiology and cell biology approaches proposed in this Coordinated Project will help to identify new drug targets as well as new chemical entities that could be the starting point for the development of new drugs for the treatment of atrial fibrillation.

The ultrafast and transiently activated potassium outward currents (IKur and Ito, respectively) are primarily responsible for the atrial repolarization process and are generated following activation of Kv1.5 and Kv4.3 channels, respectively. Ion channels form signaling complexes or channelosomes, which are essential for optimal, fast and efficient signal transmission from the extracellular or intracellular medium. IKur and Ito currents are decreased in atrial myocytes from patients with chronic atrial fibrillation; however, possible changes in the expression levels of the proteins that form the Kv1.5 and Kv4.3 channelosome have not been studied. Our group has demonstrated the existence of the Kv1.5 channelosome in rat ventricle and also in human myocardium. In addition, KChIP2, which modulates Kv4.3 channels, also interacts with Kv1.5 channels, suggesting that KChIP2 may be another component of the Kv1.5 channelosome. Over the past few years, Lgi proteins that may constitute new types of Kv accessory subunits have attracted attention. Lgi1 is able to eliminate Kvbeta1-induced rapid inactivation of Kv1.x channels, but is not expressed in human heart. We have shown that only Lgi3 and Lgi4 are present in human myocardium and that Lgi3-4 also eliminates N-type inactivation induced by Kvbeta1 subunits. Changes in the expression levels or activity of some of the proteins that make up the Kv1.5 and Kv4.3 channelosomes can have crucial pathophysiological effects and important pharmacological consequences. Therefore, in the present Research Project we propose to study, in heterologous systems and in human cardiac tissue: a) the role of KChIP2 and Lgi3-4 in the Kv1.5 and Kv4.3 channelosomes, b) the pharmacological consequences of KChIP2 and Lgi3-4 in the Kv1.5 and Kv4. 3, b) the pharmacological consequences of possible changes in the expression levels of these proteins in both channelosomes and c) the pharmacological impact of KChIP2 and Lgi3-4 on the Kv1.5 and Kv4.3 signaling complexes, using new compounds designed to interact with KChIP2 and Lgi3-4, respectively. Therefore, the results derived from this research project could help us to identify new pharmacological targets, as well as new chemical entities that could be the starting point for the development of new drugs useful in the treatment of atrial fibrillation.

Eligibility criteria

- Good academic track record.
- Research experience in electrophysiology and molecular biology.
- Highly passionate about science.
- High level of spoken and written English.

Selected publications

1. Moreno C*, de la Cruz A*, Oliveras A, Kharche SR, Guizy M, Ronchi C, Comes N, Rocchetti M, Starý T, Baró I, Loussouarn G, Zaza A, Severi S, Felipe A, Valenzuela C. Marine n-3 PUFAs modulate I_{Ks} gating, channel expression, and location in membrane microdomains. **Cardiovasc Res** 105:223-232; 2015. *: These authors equally contributed. Highlighted by the **Spanish Biophysical Society** as "Paper of the month" February 2015.
2. Moreno C*, Oliveras A*, Muñoz C, de la Cruz A, Bartolucci C, Salar E, Gimeno JR, Severi S, Felipe A, Lambiase P, Valenzuela C. A new KCNQ1 mutation at the S5 segment that impairs its association with KCNE1 is responsible for short QT syndrome. **Cardiovasc Res** 107:613-623; 2015. *: These authors equally contributed. Highlighted by the **Spanish Biophysical Society** as "Paper of the month" September 2015.
3. Naranjo JR, Zhang H, Villar D, González P, Dopazo XM, Morón J, Higueras E, Oliveros JC, Arrabal MD, Prieto A, Cercos P, González T, de la Cruz A, Casado-Vela J, Rábano A, Valenzuela C, Gutiérrez-Rodríguez M, Li J-Y,

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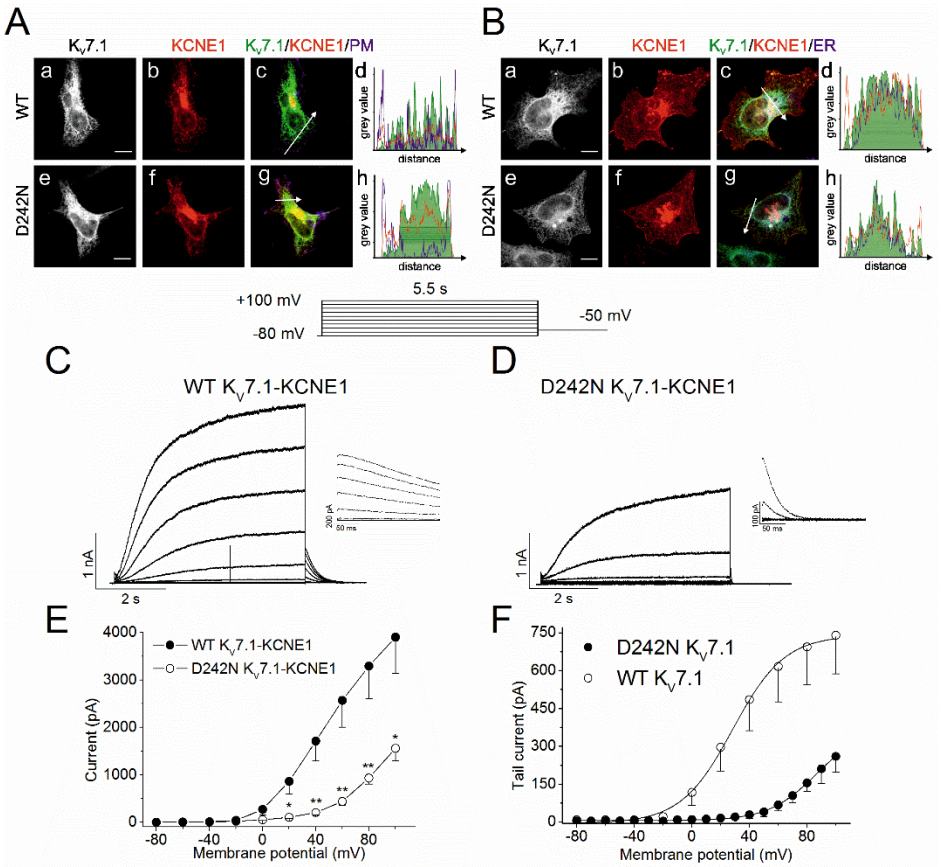
Mellström B. Activating transcription factor 6 derepression mediates neuroprotection in Huntington's disease. **JCI** 126:627-638; 2016. Highlighted in **Nature Rev Drug Discovery** 2016; 15: 160.

4. Oliveras A, Serrano-Novillo C, Moreno C, de la Cruz A, Valenzuela C, Soeller C, Comes N, Felipe A. The unconventional biogenesis of Kv7.1-KCNE1 complexes. **Science Advances** 6: eaay4472; 2020.
5. Olivencia MA*, Martínez-Casales M*, Peraza DA*, García-Redondo AB, Mondéjar-Parreño G, Hernanz R, Salaices M, Cogolludo A, Pennington MW, Valenzuela C[#], Briones AM[#]. Kv1.3 channels are novel determinants of macrophage-dependent endothelial dysfunction in angiotensin II-induced hypertension in mice. *: These authors equally contributed; [#]: Co-corresponding authors. **Br J Pharmacol** 178: 1836-1854; 2021.
6. Kiper A, Bedoya M, Stalke S, Marzian S, Ramírez D, de la Cruz A, Peraza DA, Vera-Zambrano A, Márquez Montesinos JCE, Arévalo Ramos BA, Rinné S, Gonzalez T, Valenzuela C*, Gonzalez W*, Decher N*. Identification of a critical binding site for local anesthetics in the side pockets of Kv1 channels. *: Co-corresponding authors. **Br J Pharmacol** 178: 3034-3048; 2021.
7. Díaz del Campo L, García-Redondo AB, Duro-Sánchez S, Zaragoza C, Palmas F, Peraza DA, de Benito-Bueno A, Socuéllamos PG, Rodrigues-Diez R, Valenzuela C, Dalli J, Salaices M, Briones AM. Treatment with resolvin D2 attenuates cardiovascular damage in angiotensin II-induced hypertension. **Hypertension** 80(1):84-96; 2023.
8. Peraza DA, Povo-Retana A, Mojena M, García-Redondo AB, Avilés P, Boscá L, Valenzuela C. Trabectedin modulates the macrophages polarization in the tumor-microenvironment. Role of K_V1.3 and K_V1.5 channels. **Biomed & Pharmacotherapy** 161: 114548; 2023.



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