COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2023/2024

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☐ **Requested** ☒ **Acquired**	**Funding origin: ANR grant**
Thesis title: **Wireless implantable devices for optical control of cardiac rhythm with a photoactivable peptide**		3 keywords: therapy, cardiac arrhythmias, photopharmacology
Unit / team: **l'insitut du thorax**		
Supervisor's name: **Flavien Charpentier / Jerome Montnach**		Phone number: +33 2 28 08 01 34 Email address: Jerome.montnach@univ-nantes.fr

Socio-economic and scientific context (approximately 10 lines):

Sudden cardiac death is a major cause of death worldwide. The cardiac arrhythmias that cause sudden death involve dysfunction of ion channels, the building blocks of cardiac electrical activity. Despite their effectiveness, current therapeutic approaches are not targeted. The identification of new targets and compounds that safely and effectively prevent the onset of arrhythmias, by enabling spatio-temporal control of their action, represents a major challenge. On the one hand, peptides derived from animal toxins (whether inhibitory or activating) are among the most suitable compounds for targeting cardiac ion channels with high affinity and selectivity. On the other hand, our group and others have demonstrated that innovative photopharmacological approaches can control the spatio-temporal activity of compounds targeting ion channels. Combining peptides derived from natural toxins with photopharmacological approaches offers a unique opportunity to monitor ion channel activity with high spatio-temporal resolution in cardiac regions of interest, in order to identify arrhythmogenic targets and propose new therapeutic avenues.

Working hypothesis and aims (approximately 8 lines):

The myocardium is not a homogeneous structure in terms of ion channel expression and hence cardiac electrical activity. This heterogeneity, which is still poorly understood, is essential to the proper functioning of the heart, but is also at the root of cardiac arrhythmias. In order to better understand the mechanisms involved and ultimately propose new therapeutic approaches, a precise study of arrhythmogenic zones is necessary. Among the ion channels identified as having a role in the generation of arrhythmias, tetrodotoxin-sensitive sodium channels (TTX-S) appear to play an important role. Their activation is arrhythmogenic, and their inhibition would prevent arrhythmias of various origins. However, due to a lack of tools, no studies have selectively targeted these channels. Based on peptides that selectively target these channels, we have developed photoactivatable analogues that activate or inhibit these peptides via the action of light, with strong spatio-temporal control. We have demonstrated the efficacy of this approach in vitro, ex vivo and in vivo. In this thesis, we hypothesize that in vivo modulation of these channels using cardiac implants will validate the cardiac photopharmacology approach, and that spatio-temporal control of channel activity will enable us to identify arrhythmogenic zones and better understand their characteristics.

Main milestones of the thesis (approximately 12 lines):

- Optical control of the activity of a peptide targeting TTX-S channels and having demonstrated its arrhythmogenic potential through the use of optical cardiac implants.

- Identification of arrhythmogenic zones by localized activation of TTX-S channels on isolated rat heart by modulating the size and number of optically targeted regions.

- Development of in vivo spatio-temporal control of TTX-S channel activation in defined arrhythmogenic zones.

- Study of the functional relationship between TTX-S channel modulation and calcium homeostasis using cardiac optical mapping.

- Functional validation of new photopharmacological approaches (patch-clamp) using visible or near-infrared light.

- Demonstration of the feasibility of the cardiac photopharmacology approach in large animals.

Scientific and technical skills required by the candidate (2 lines):
Technical skills with rodents, cardiac electrophysiology (patch-clamp, ecg, ...), analysis of electrophysiological data in vitro, ex vivo and in vivo, Langendorff and cardiac mapping, basic biochemical techniques, confocal microscopy and histology. Surgical skills are not required for application.

3 publications from the team related to the topic (last 5 years):

1. Montnach J, Blömer LA, Lopez L, Filipis L, Meudal H, Lafoux A, Nicolas S, Chu D, Caumes C, Béroud R, Jopling C, Bosmans F, Huchet C, Landon C, Canepari M, De Waard M. In vivo spatiotemporal control of voltage-gated ion channels by using photoactivatable peptidic toxins. Nat Commun. 2022 Jan 20;13(1):417. doi: 10.1038/s41467-022-27974-w. PMID: 35058427; PMCID: PMC8776733.

2. Lopez L, Montnach J, Oliveira-Mendes B, Khakh K, Thomas B, Lin S, Caumes C, Wesolowski S, Nicolas S, Servent D, Cohen C, Béroud R, Benoit E, De Waard M. Synthetic Analogues of Huwentoxin-IV Spider Peptide With Altered Human NaV1.7/NaV1.6 Selectivity Ratios. Front Cell Dev Biol. 2021 Dec 20;9:798588. doi: 10.3389/fcell.2021.798588. PMID: 34988086; PMCID: PMC8722715.

3. Montnach J, De Waard S, Nicolas S, Burel S, Osorio N, Zoukimian C, Mantegazza M, Boukaiba R, Béroud R, Partiseti M, Delmas P, Marionneau C, De Waard M. Fluorescent- and tagged-protoxin II peptides: potent markers of the Nav 1.7 channel pain target. Br J Pharmacol. 2021 Jul;178(13):2632-2650. doi: 10.1111/bph.15453. Epub 2021 May 14. PMID: 33742442.

National and international collaborations: **Philipp Gutruf (University of Arizona)**