CMD InnoCARE (Innovation pour les maladies CArdiovasculaires, métaboliques et REspiratoires)

Master 2 Internship proposal (2024-2025)

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Profile(s) linked to the project:
☒ Experimental Biology *(Recherche expérimentale)*
☐ Research and Biological Data Analysis *(Recherche et analyse de données biologiques)*
☐ Clinical Research *(Recherche clinique)*

Lab: *l'institut du thorax* research unit

Team: Ion channels and cardiopathies

Name and position of the supervisor: Flavien Charpentier

Email of the supervisor: flavien.charpentier@univ-nantes.fr

Candidate (if known): Mattéo GAULT

Title of the internship: Effects of an AAV-9 encoding a truncated form of the Nav1.8 channel on a mouse model of cardiac conduction disorders.

Summary of the internship proposal:

The Brugada syndrome (BrS) is a rare cardiac arrhythmic disease that is suspected to account for more than 20% of sudden cardiac deaths (SCD) in patients without structural heart disease and 4-12% of SCD in the general population. Currently, the only therapy is the implantation of a defibrillator (ICD) in patients identified as being at highest risk of SCD. However, this risk is difficult to estimate for asymptomatic patients. Moreover, ICD are associated with a risk of complications of about 30% at 10-year follow-up. There is thus a need for developing alternative therapeutic strategies.

In 25-30% of cases, BrS is due to mutations in *SCN5A*, which codes the voltage-gated Na^+ channel Nav1.5, or in genes coding Nav1.5 regulatory subunits. These mutations, transmitted in a dominant autosomal mode, lead to a decrease of functional Nav1.5 at the cell membrane. Recently, a naturally occurring cardiac-specific short transcript of *SCN10A* (SCN10A-short, here designated S10s) was discovered. It modulates the density of the Nav1.5-mediated Na^+ current. Loss of S10s expression was found to slow cardiac conduction in mice and reduce I_{Na} in isolated cardiomyocytes, while overexpression of S10s in HEK293 cells stably expressing *SCN5A* increased I_{Na}.

In this context, our project is to overexpress S10s in a mouse model of BrS due to *Scn5a* haploinsufficiency, the *Scn5a* heterozygous knockout mouse (*Scn5a*+/-), using an adeno-associated virus AAV-9, and evaluate its putative therapeutic effects. The objectives of the recruited Master 2 student will be:

1. to quantify S10s expression in the heart and in other organs, such as liver, using western blot technique;
2. to determine the level of heterogeneity of S10s expression in cardiac myocardium using immunostainings;
3. to determine the functional consequences of S10s expression on cardiac electrical activity on Langendorff-perfused mouse hearts using optical mapping technique.

Intravenous injection of the AAV-9 and *in vivo* functional studies will be performed by trained technicians.

Form to be sent by email to gpinnocare@univ-nantes.fr