DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

Année 2024 /2025

FICHE SUJET DE THESE

Sujet N° (à remplir par l'ED) :	**FINANCEMENT :** ☐ **Demandé** ☒ **Acquis**	**Origine du financement : EIC Pathfinder NaV1.5-CARED**
Titre de la thèse : **HC-NU-NaV1.5 regulation fine-tuning as a therapy for cardiac Conduction And Arrhythmic diseases at Risk of sudden Death**		3 mots-clés : genetics, sudden cardiac death, cardiomyocytes derived iPSC
Unité/équipe encadrante : **Inserm UMR 1087/CNRS UMR 6291 Équipe I : Génétique cardiovasculaire - JJ Schott – R Redon**		
Directeur de thèse : **Jean-Jacques Schott**		N° de tél : 0228080151 Mail : Jean-Jacques.Schott@univ-nantes.fr

Contexte socioéconomique et scientifique (env. 10 lignes) :

The voltage-gated sodium channel (Na-channel; NaV1.5) is a central component of cardiac electrogenesis. Its dysfunction can lead to arrhythmias (ventricular fibrillation, VF) that cause sudden cardiac death. While NaV1.5 represents a highly relevant therapeutic target for prevention of life-threatening cardiac arrhythmias, therapies that target the expression or function of this channel are non-existent.

The NaV1.5-CARED project will capitalise on the recent work, that has shown the utility of genetic studies in cohorts of deeply phenotyped patients with cardiac electrical and conduction defects to uncover regulatory regions and proteins partner that modulate the expression and function of NaV1.5. This project aims also to validate and develop innovative therapies to restore the function of NaV1.5. This will, for the first time, provide an alternative for the invasive and costly implantation of cardioverter defibrillator (ICD) or pacemaker (PM) implantation therapies currently used. In parallel, NaV1.5-CARED will leverage insights into the genetic factors that impact cardiac arrhythmia to refine genetic testing in patients and provide a relevant risk stratification or a predictive disease pathway on an individual basis. The rare cardiac disorders associated risk of SCD provide a powerful setting for identification of genetic factors that impact conduction also in individuals from the general population and could then lead to, through polygenic risk score (PRS), a preventive clinical care management. Concerning therapy, current arrhythmia preventive strategies in high-risk patients rest on device implantation. However, ICD or PM therapy leads to major complications in 4% to 15% of the patients. Current preventive health strategies coupled to population aging will lead inexorably to the increase of device implantation and as a consequence, a growing cost for the society (cost-effectiveness is about 12-16 k€ / Patient-Year). Cardiac gene therapy holds the potential to transform the way we treat patients with cardiac channelopathies and acquired arrhythmias with the ultimate goal to reduce the burden of device therapy-related complications and improvement in overall patient outcomes.

Hypothèses et questions posées (env. 8 lignes) :

We therefore aim for a triple objective:

1) predict the risk of (fatal) arrhythmia at the individual level by developing adapted PRS to better identify patients requiring device implantation,

2) characterize the molecular mechanism associating non-coding regulatory regions and the electrical cardiac pathogenesis to uncover new therapeutic targets,

3) and develop new candidates for therapeutic intervention able to restore Na+ current loss of function.

Grandes étapes de la thèse (env. 12 lignes) :

NaV1.5-CARED aims, based on the unique complementary expertise gathered in this project, to identify actionable variants, group of variants by extending successful genetic study on the largest worldwide clinical databases and bio-collection of population of patients but also priceless large familial cases presenting BrS, an inherited ventricular arrhythmia syndrome and cardiac conduction defects (CCD).

To reach this objective we will generate an unprecedent genotyping and genomic datasets consisting of >20 000 cases-controls whole genome genotyped allowing to interrogate > 7 000 000 common variants per individual, > 3200 cases-controls whole genome sequence interrogating for the first time in such large population rare and low frequency variants as well as large rearrangements and > 100 SCN5A carrier families corresponding to > 1200 individuals in whom long reads sequencing will uncover the haplotype phase between rare and common variants. Thanks to these large population and family sets combined with comprehensive genomics approaches, we will be able to describe specific risk genetic markers and associated molecular mechanisms according sex differences, age of patient and clinical history.

Furthermore NaV1.5-CARED will implement personalized (age, sex, clinical history, genetic background specific) PRS to translate identified genetic markers to clinical use and stratify the risk of arrhythmia for adapting care management and identify patients requiring ICD implantation.

Based on the genome wide studies proposed by NaV1.5-CARED, we will identify potential new therapeutic targets such as non-coding cardiac regulatory regions and novel NaV1.5 gene-protein partners. We will evaluate their impact on the NaV1.5 expression level, intracellular/membrane location and on the Na+ current density thanks to innovative human cardiomyocyte dedicated screening models developed in the context of NaV1.5-CARED. This screening will be also the opportunity to implement innovative and high-throughput screening methods adapted to efficiently provide the first proof of concept for novel innovative therapy strategies.

As an illustration of the expertise gathered in NaV1.5-CARED project, recent studies from 3 partners of NaV1.5-CARED made emerge for the first time, an endogenous molecule (SCN10A-Short) able to rescue Na+ current loss of function and conduction defects. Then NaV1.5-CARED aims to further validate using in vivo animal models this molecule as well as the most pertinent innovative strategies and molecules identified with our screening pipeline.

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Compétences scientifiques et techniques requises par le candidat (2 lignes) :
Génétique, épigénétique, culture cellulaire d'iPSC, différenciation en cardiomyocytes, genome editing, physiologie cardiaque, biologie moléculaire, intérêt pour les analyses et interprétations de données issus de la nouvelle génération de séquençage

3 publications de l'équipe d'accueil relatives au domaine (5 dernières années) :

1. Brugada syndrome in Japan and Europe: a genome-wide association study reveals shared genetic architecture and new risk loci.
Ishikawa T, Masuda T, Hachiya T, Dina C, Simonet F, Nagata Y, Tanck MWT, Sonehara K, Glinge C, Tadros R, Khongphatthanayothin A, Lu TP, Higuchi C, Nakajima T, Hayashi K, Aizawa Y, Nakano Y, Nogami A, Morita H, Ohno S, Aiba T, Krijger Juárez C, Mauleekoonphairoj J, Poovorawan Y, Gourraud JB, Shimizu W, Probst V, Horie M, Wilde AAM, Redon R, Juang JJ, Nademanee K, Bezzina CR, **Barc J**, Tanaka T, Okada Y, **Schott JJ**, Makita N. *Eur Heart J. 2024*

2. Left Ventricular Abnormal Substrate in Brugada Syndrome.
Cheniti G, Haissaguerre M, Dina C, Kamakura T, Duchateau J, Sacher F, Racine HP, Surget E, Simonet F, Gourraud JB, Sridi S, Cochet H, Andre C, Bouyer B, Chauvel R, Tixier R, Derval N, Pambrun T, Dubois R, Jais P, Nademanee K, Redon R, ***Schott JJ****, Probst V, Hocini M,* ***Barc J****, Bernus O. JACC Clin Electrophysiol. 2023*

3. Genome-wide association analyses identify new Brugada syndrome risk loci and highlight a new mechanism of sodium channel regulation in disease susceptibility*.*
Barc J, Tadros R, Glinge C, Chiang DY, Jouni M, Simonet F, Jurgens SJ, Baudic M, Nicastro M, Potet F, Offerhaus JA, Walsh R, Choi SH, Verkerk AO, Mizusawa Y, Anys S, Minois D, Arnaud M, Duchateau J, Wijeyeratne YD, Muir A, Papadakis M, Castelletti S, Torchio M, Ortuño CG, Lacunza J, Giachino DF, Cerrato N, Martins RP, Campuzano O, Van Dooren S, Thollet A, Kyndt F, Mazzanti A, Clémenty N, Bisson A, Corveleyn A, Stallmeyer B, Dittmann S, Saenen J, Noël A, Honarbakhsh S, Rudic B, Marzak H, Rowe MK, Federspiel C, Le Page S, Placide L, Milhem A, Barajas-Martinez H, Beckmann BM, Krapels IP, Steinfurt J, Winkel BG, Jabbari R, Shoemaker MB, Boukens BJ, Škorić-Milosavljević D, Bikker H, Manevy FC, Lichtner P, Ribasés M, Meitinger T, Müller-Nurasyid M; KORA-Study Group, Veldink JH, van den Berg LH, Van Damme P, Cusi D, Lanzani C, Rigade S, Charpentier E, Baron E, Bonnaud S, Lecointe S, Donnart A, Le Marec H, Chatel S, Karakachoff M, Bézieau S, London B, Tfelt-Hansen J, Roden D, Odening KE, Cerrone M, Chinitz LA, Volders PG, van de Berg MP, Laurent G, Faivre L, Antzelevitch C, Kääb S, Arnaout AA, Dupuis JM, Pasquie JL, Billon O, Roberts JD, Jesel L, Borggrefe M, Lambiase PD, Mansourati J, Loeys B, Leenhardt A, Guicheney P, Maury P, Schulze-Bahr E, Robyns T, Breckpot J, Babuty D, Priori SG, Napolitano C; Nantes Referral Center for inherited cardiac arrhythmia, de Asmundis C, Brugada P, Brugada R, Arbelo E, Brugada J, Mabo P, Behar N, Giustetto C, Molina MS, Gimeno JR, Hasdemir C, Schwartz PJ, Crotti L, McKeown PP, Sharma S, Behr ER, Haissaguerre M, Sacher F, Rooryck C, Tan HL, Remme CA, Postema PG, Delmar M, Ellinor PT, Lubitz SA, Gourraud JB, Tanck MW, George AL Jr, MacRae CA, Burridge PW, Dina C, Probst V, Wilde AA, **Schott JJ**, Redon R, Bezzina CR. *Nat Genet. 2022.*

Collaborations nationales et internationales :

- Prof. Connie Bezzina; University of Amsterdam's Faculty of Medicine, Amsterdam, The Netherlands
- Prof. Vincent Christoffels, University of Amsterdam's Faculty of Medicine, Amsterdam, The Netherlands
- Dr. Sebastian Diecke, MDC, BErlion, Germany
- Dr. Rafik Tadros, Montreal Heart Institute, Montreal, Quebec, Canada
- Prof. Michel Haissaguerre, IHU LIRYC, Electrophysiology and Heart Modeling Institute, Bordeaux, France.
- Prof. Makita Naomasa; National Cerebral and Cardiovascular Center Osaka, Japan
- Prof. E. Gandjbakhch, Institut de Cardiologie CHU Pitie Salpêtrière, Inserm 1166, Paris, FR