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 :**
Titre de la thèse : **C-UN- identification and characterization of the genetic factors underlying the idiopathic ventricular fibrillation**		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) :
In approximately 6-10% of survivors of sudden cardiac arrest (SCA), no specific cause can be found after comprehensive clinical evaluation. Current guidelines recommend a complete workup - including pharmacological testing - among unexplained SCA survivors and emphasize the importance of multidisciplinary services with cardiac genetic expertise in their diagnostic evaluation. Unexpected sudden death due to documented ventricular fibrillation and without established diagnosis after extensive clinical evaluation is referred as idiopathic ventricular fibrillation (IVF). The absence of diagnosis annihilates any preventive strategy expect from the implantation of a defibrillator (ICD) in primary prevention. However, Besides the cost for the society (cost-effectiveness is about 12-16 k€ / Patient-Year), ICD therapy is far from an ideal treatment, since its implantation represents an invasive intervention, which can be a source of major complications for 4% to 15% of the patients implanted such as infection after the first or the replacement intervention, complications related to lead dislodgement or myocardial perforation. Furthermore, 20% of the patients implanted and suffering from anxiety-depression present an increased mortality mainly related to the possibility receiving an ICD shock.

Challenge then resides in identifying the clinical aetiology to propose an adapted clinical management and prevent the risk of SCA. Invasive electrophysiological investigation in IVF patients and more recently the analysis of episode of ventricular fibrillation recorded by the defibrillator suggest that IVF patients could be categorized into 2 groups. Ventricular fibrillation may be the consequence of abnormal electrical activity from the Purkinje conduction system or due to myocardial structural abnormalities.

In parallel, significant progress in the description of the genetic architecture of inherited primary electrical disorders and cardiomyopathies have been performed thanks to genome wide association studies (GWASs) performed on large patient populations. These studies provide singular molecular signature based on the presence of specific combination of common variants associated with the disease.
The contribution of common variants in inherited cardiac disorders is completing the knowledge accumulated so far with the description of the role of rare variants in these diseases.

Hypothèses et questions posées (env. 8 lignes) :

The aim of our study is to describe the distinct genetic background underlying IVF associated with a Purkinje or myocardial structural substrate. The ultimate aim of this thesis is to be able to classify and propose an aetiology for IVF patients based on genetic background of patients and adapt the clinical management to avoid SCA in patient and its relatives.

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

Based on the largest worldwide IVF databases and biobank representing >700 unrelated IVF cases of whom 450 have been classified as "Purkinje" or "myocardial structural abnormality" after invasive electrophysiology mapping, exome or WGS will be performed to assess the prevalence of primary electrical disorders or cardiomyopathy associated genes. Burden testing will be applied on both group to uncover new genes associated with a potential specific pathways related to Purkinje substrate.

In parallel, patients will be genotyped and GWAS will be performed to uncover either specific genetic architecture/signature or to compare genetic background with other cardiac inherited disorders (multi-traits analysis of GWAS).

Functional studies, using genome editing on human iPSC derived cardiomyocytes are required to disclose the role of the genes/regulatory region identified. This approach run in routine in the group will allow to perform 1) functional annotation of the genome to locate and characterize the role of the non-coding region associated with the phenotype, 2) identify the molecular mechanisms associating these non-coding/regulatory regions to target genes and 3) conduct functional analysis to characterize the role of these genes in the cardiac pathophysiology.

This project owns an international component through the collaboration with the group of Rafik Tadros, Montreal Heart Institute, Montreal, Quebec, Canada. This collaboration in the context of genome wide studies has been recently successful and led recently to the publication of an article in Nature Genetics (DOI: 10.1038/s41588-021-01007-6).

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. *TAD boundary deletion causes PITX2-related cardiac electrical and structural defects*

Baudic M, Murata H, Bosada FM, Souto Melo, U, // , Mundlos S, Christoffels VM, Probst V, ***Schott JJ, Barc J****. Nat. Commun. (accepted)*

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 :

- Dr. Rafik Tadros, Montreal Heart Institute, Montreal, Quebec, Canada
- Prof. Michel Haissaguerre, IHU LIRYC, Electrophysiology and Heart Modeling Institute, Bordeaux, France.
- Prof. Connie Bezzina; University of Amsterdam's Faculty of Medicine, Amsterdam, The Netherlands
- Prof. Makita Naomasa; National Cerebral and Cardiovascular Center Osaka, Japan
- Prof. Mundlos Stephan at the Max Planck institute for Molecular genetics in Berlin, Germany
- Prof. E. Gandjbakhch, Institut de Cardiologie CHU Pitie Salpêtrière, Inserm 1166, Paris, FR
- Prof Lia Crotti, Istituto Auxologico Italiano IRCCS, Milan, IT