## THESIS TOPIC

<table>
<thead>
<tr>
<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
<th>Funding origin: NEXT-IRP VERACITIES</th>
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<tr>
<td>Thesis title: HCU-UN-Cardiac Regulome Impairment: New Mechanisms For Ventricular Arrhythmia Associated With Sudden Cardiac Death</td>
<td>3 keywords: genetics, epigenetics, cardiovascular physiology</td>
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<td>Unit / team: Inserm UMR 1087 / CNRS UMR 6291</td>
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### Socio-economic and scientific context (approximately 10 lines):

Nowadays, the technological development in genomics allows exploring the whole spectrum of the human genetic variations, from rare to common, within the coding (2%) and non-coding (98%) regions of the genome. The access to such pan-genomic data, for a continuously decreasing cost, opens new research prospects and will result in the development of a predictive medicine. The implementation of such molecular medicine implies to be able to interpret the consequences of the genetic variants thus uncovered with a particularly challenging effort for those located within the non-coding regions of the genome. Predictive medicine is especially expected in the context of the sudden cardiac death (SCD) since the majority of the victims are individuals from the general population free from forewarning sign of SCD. The lack of relevant biological and clinical marker does not allow any preventive screening and early diagnosis and leads to the occurrence of about 50 000 SCD per year in France. Remarkably, a common mechanism: the ventricular fibrillation (VF) is actually encountered in 80-90% of the SCD cases whatever the etiology. Interestingly, 5 to 10% of SCD cases present no structural heart defect after post mortem examination and are classified among the lone VF population. Among them we found the Brugada syndrome (BrS) (OMIM#601144) which may particularly be considered as ‘sensitized models’ for SCD/VF genetic marker discovery and be relevant to the broad problem of SCD.

### Working hypothesis and aims (approximately 8 lines):

The lack of relevant markers for SCD led us to investigate the non-coding regions of the genome, seats of gene regulation. By extending our previous Brugada Syndrome (BrS) genome wide association study (Bezzina et al Nat Genetics 2013) with today, the largest worldwide BrS collection (>2800 BrS cases recruited over 40 international centres), we identified 21 variants (all located in non-coding regions) that increase dramatically the risk to develop the disease and are likely relevant to the broad problem of SCD. Among them, six are pointing to transcription factors (TF), suggesting a strong involvement of the transcriptional regulation in cardiac arrhythmia diseases. However converting the genetic findings to molecular mechanisms is challenging since signals identified are located within non-coding regions.

### Main milestones of the thesis (approximately 12 lines):

Hence, using human cardiomyocytes derived from induced pluripotent stem cells (iPSCs), the project aims to firstly characterize the human cardiac regulome by identifying the cardiac gene regulatory regions (GRRs) using ATAC-seq and ChIP-seq approaches and the nature and location of the major cardiac transcription factors (TF) implicated in gene regulation. We will then specifically investigate the 21 BrS loci by identifying the GRRs associated to the GWAS signals and the TF binding sites affected. We also aim to decipher the pathophysiological consequences on the phenotype by performing chromatin conformation experiments to identify the gene target(s) of the GRR and perform a transcriptomic study to appreciate the impact on the gene target expression. The next steps would consist into characterizing their impact on cardiac electrical activity in a pathophysiology context.

### Scientific and technical skills required by the candidate (2 lines):

Genetics/epigenetics, cardiac physiology, molecular biology, interest for big-data analysis.

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


### National and international collaborations:

- Prof. Mundlos, Max Planck institute for Molecular genetics, Berlin, Germany
- Prof. A. Wilde and Prof. C. Bezzina, Academic Medical Center, Amsterdam, NL
- Dr. E.R. Behr, St George's University of London, UK
- Prof. S. Mundlos, Max Planck institute, Berlin, DE
- Dr. J. Poschmann, CRTI, Nantes

Extensive collaboration in the setting of the Brugada Syndrome GWAS network:

(Prof Wilde, Academic Medical Center, Amsterdam, The Netherlands; Dr Behr, St. George's Hospital, University Of Londres, UK; Prof Leenhardt, Service de Cardiologie et Centre de Référence des Maladies Cardiaques Héréditaires, Hôpital Bichat, Paris, France; Prof Schulze-bahr, Department of Cardiology and Angiology Hospital of the University of Münster, Germany; Prof Kaab Ludwig Maximilian Universität, Munich)
Germany; Prof Schwartz Department of Cardiology at the University of Pavie, Italy; Prof Roden, Vanderbilt University School of Medicine Nashville, USA; Prof Antzelevitch, Department of Experimental Cardiology, Utica, New York, USA; Prof Tfelt-Hansen, Department of Cardiology, the Heart Center, Copenhagen, Denmark; Prof Horie, Department of Cardiovascular Respiratory Medicine, Otsu, Japan; Prof Makita, Department of Molecular Physiology, Nagasaki, Japan; Prof Shimizu, Department of Cardiovascular Medicine, Tokyo, Japan; Dr D. Nuyens, Leuven, Belgium; Dr. J Saenen, Antwerp, Belgium; Dr. M. Borggrefe, Mannheim, Germany; Prof Priori, Pavie, Italy and Prof Gaita, Turin, Italy).