

# *Normal Cardiac Excitation: Generation, Propagation and Coupling to Contraction*

**Acronym:** NORMACOR

**Duration:** 36 months

**Starting date:** 01/09/2006

**Instrument:** STREP

## **SUMMARY**

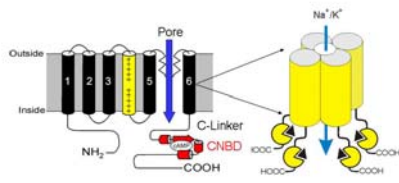
Cardiac arrhythmia is a major cause of morbidity and mortality in Europe and of growing socio-economic concern. Recent data suggest that novel mechanisms such as HCN channels, mechanical effects on Ca handling and ion flux balances, and cellular heterogeneity may trigger and/or permit the sustenance of arrhythmias. The novelty of our approach is to focus on these potentially crucial, but ill-investigated, mechanisms by uniting 8 leading labs from 5 EU countries who focus on individual arrhythmogenic aspects, in a bid to combine their expertise and shed light on how physiological or compensatory mechanisms may turn arrhythmogenic, and how this may be controlled or corrected.

Prime targets are structured along three levels of functional integration:

- Membrane level: Role of HCN channels in the generation of normal and abnormal rhythm
- Cellular level: Role of electro-mechanical interaction in modulating contractile activity and electrophysiology.
- Multicellular level: Role of heterogeneity in normal and remodelled tissue on electrical excitation and conduction.

**SCIENTIFIC AND TECHNOLOGICAL OBJECTIVES:**

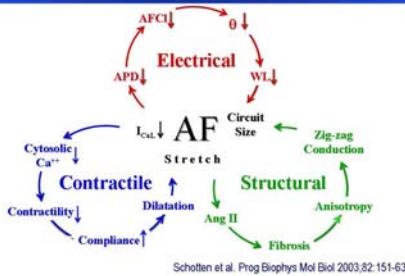
**The HCN Channel Family**



Ludwig et al. (1998) Nature 393:587-591

- To develop suitable experimental tools, including HCN transgenic mice, novel bradycardic and antiarrhythmic agents, control of mechano-electrical interactions, and the symbiosis of the above;

**The Three Wheels**

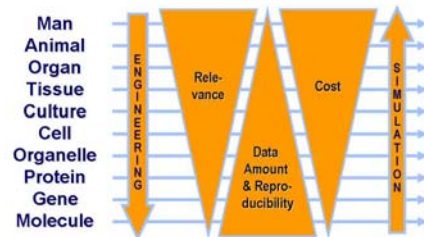


Scholten et al. Prog Biophys Mol Biol 2003;82:151-63

- To acquire new knowledge on molecular mechanisms and pathways controlling generation and spread of excitation in normal and diseased cardiac tissue;

- To combine advanced engineering techniques for ‘top-down’ development of novel experimental tools with mathematical ‘bottom-up’ integration of data from the molecular level to fundamental and clinical relevance.

**Model vs. Hypothesis Driven Research**



Koh, Bollensdorff & Garry. Exp Physiol 2006;91:307-321.

Based on the combination of skills and techniques not currently available in any single lab worldwide, we will provide novel insight into novel arrhythmogenic mechanisms, quantify their interrelation, target preventive and therapeutic interventions to reduce the societal and economical impact of cardiac arrhythmia.

## **PROBLEM**

This project faces several problems dealing with relevant EC societal and policy objectives:

the discovery of new antiarrhythmic strategies and the identification of vulnerable parameters (proteins and pathways) tricking the propensity to abnormal cardiac excitation, as it occurs in a variety of cardiac diseases associated to high arrhythmic propensity (heart failure, diabetes, hypertension);

development of novel drugs able to prevent cardiac arrhythmias or reduce the propensity to recurrence/chronicization of them, thus improving the quality of life and health.

## **AIM:**

This **STREP** is a research and technological development project which brings together 8 expert European research laboratories in 5 different EU countries and integrates a range of multidisciplinary investigations into cardiac arrhythmia mechanisms and ion channel exploration. Measurable and verifiable scientific and technological objectives can be summarized as follows:

- to **develop suitable experimental tools**, including HCN transgenic mice, novel bradycardic and antiarrhythmic agents, control of mechano-electrical interactions, and the symbiosis of the above;
- to **acquire new knowledge** on molecular mechanisms and pathways controlling generation and spread of excitation in normal and diseased cardiac tissue, and
- to **combine advanced engineering techniques** for 'top-down' development of novel experimental tools with mathematical 'bottom-up' integration of data from the molecular level to clinical relevance.

## **EXPECTED RESULTS:**

The expected result consists in the development of new experimental tools for studying normal/abnormal rhythm generation, such as:

- HCN Transgenic animals.
- HCN-selective bradycardic drugs.
- Generation of a biological pacemaker.

- Application of the single-myofibril technique to perform mechanical experiments in samples from human and animal hearts.
- Adaptation of the multi-microelectrode array technique to sections of animal and human atrial tissue.

#### **POTENTIAL APPLICATIONS:**

**Scientific advancements** will consist in the elucidation of molecular mechanisms and pathways controlling rhythm generation and electrical propagation in healthy and diseased cardiac tissue, such as:

a) Role of HCN channels in the generation of normal and abnormal rhythm. Three strategies will be used: i) assessment of the molecular composition and sub-cellular localization of native HCN channels ; ii) effect of mislocalization, over-expression, or abolition of cardiac HCN channels in terms of altered pacemaking or cardiac conduction, and propensity to arrhythmias in the normal and diseased heart; iii) identification of cardiac channelopathies linked to mutations of human HCN channels.

b) Integrated knowledge of electrical and structural atrial remodelling. The project will address the relationship among electrical, contractile and conduction abnormalities in atrial cells/tissues challenged with different stressing conditions (in-vivo atrial pacing, in-vitro mechanical stimulation and axial stretch, exposure to neurohumoral factors such as endothelin-1) and in human atrial specimens.

Societal advancements and applications are the discovery of new antiarrhythmic strategies and the identification of vulnerable parameters (proteins and pathways) tricking the propensity to abnormal cardiac excitation, as it occurs in a variety of cardiac diseases associated to high arrhythmic propensity (heart failure, diabetes, hypertension). The final objective is to propose newly developed drugs and/or therapeutic strategies aimed to prevent cardiac arrhythmias or reduce the propensity to recurrence/chronicization of them, thus contributing to quality of life and health and to reduce the socio-economic impact of cardiac diseases. Finally, the project will contribute to educational training and mobility in Europe, as a number of young researchers, both postgraduate and postdoctoral, will be employed to carry out the research.

**Project web-site:** <http://www.NormaCOR.eu>

**Key words:** cardiac arrhythmias, hyperpolarization-activated channels, channelopathies, atrial fibrillation, pacemaking, cardiac remodelling, transgenic mice, myofibrils, modelling tools.

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