

Heartbeat is the rhythm of life

Keeping the most efficient, natural machine in order...

Cardiac arrhythmia is a major cause of morbidity and mortality in Europe and of growing socioeconomic concern. Management of arrhythmias requires complex and expensive therapeutic interventions that include drugs, invasive procedures, devices and surgery. Notwithstanding clinical evolution, common side effects of antiarrhythmic agents and cost of implantable devices drive unrelenting investigations into cardiac electrophysiology, aimed at preventing/treating arrhythmias and improving patient care.

On this basis, we created a consortium of eight leading laboratories from five countries, in a bid to combine our expertise and shed light on how physiological or compensatory mechanisms may turn arrhythmogenic, and how this may be controlled or corrected. NormaCOR (Normal Cardiac Excitation: Generation, Propagation and Coupling to Contraction) is an FP6 strategic project funded in 2006 by the European Commission. In the last three years, NormaCOR members conducted multifaceted research to improve basic knowledge on arrhythmogenic mechanisms, design and test novel drugs and integrate different experimental approaches.

HCN channels and the control of heart rhythm

Beating about 100,000 times a day, the human heart is one of the most efficient natural machines. This extraordinary performance relies on the heart's ability to beat spontaneously. A major contributor to the initiation of heartbeats is an ionic current, expressed namely in pacemaker cardiac cells and coded by HCN (Hyperpolarization-activated Cyclic Nucleotide-gated) genes.

Its role and properties make this current an ideal target to study with the aim

of improving our understanding of pacemaker activity and using this knowledge in clinically-relevant applications. Thanks to the leading contribution of Dario DiFrancesco and co-workers (Mirko Baruscotti Andrea Barbuti) in Milan and Martin Biel in Munich, we advanced basic knowledge on the genetic of rhythm disorders caused by dysfunctional HCN channels and created transgenic mouse lines modelling human cardiac diseases. Research on HCN-selective drugs brought the synthesis of new molecules with unique block properties, recently patented by the Co-ordinator Elisabetta Cerbai with the Pharmaceutical Chemist M Novella Romanelli (Florence) as antiarrhythmic and bradycardic agents.

Atrial fibrillation: modelling and remodelling

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 4% of the population over 60 years of age, with a significantly increased morbidity and high medical costs. Three work packages were designed to facilitate dynamic exchange among partners specifically dedicated to this field: Ursula Ravens and Erich Wettwer in Dresden, Ulrich Schotten in Maastricht, Andras Varro in Szeged and Corrado Poggesi in Florence. Studies performed in our labs shed light on a greatly challenging vicious cycle termed 'remodelling'. It occurs because of persistence of atrial fibrillation and, in doing so, it promotes AF chronification. We combined bench studies in human atrial samples and animal models of AF made available for the project, and implemented innovative experimental approaches. Overall, information on electrical and contractile remodelling, which renders the cell largely insensitive to common drugs, is suggestive of novel pharmacological strategies, such as control of

excitation-contraction coupling mechanisms studied by David Eisner and Andrew Trafford in Manchester, and myofilament calcium sensitivity. The experimental data of the consortium served as input for mathematical models developed by Peter Kohl and his group (Oxford), which are suited for in silico predictions of drug effects on cardiac electrogenesis. Collaborations and exchange programmes among partners in Dresden, Manchester, Oxford and Szeged led to the development of new techniques and models proving novel insight into the mechanisms of arrhythmia.

These results and plans for their dissemination were discussed during the final meeting of the NormaCOR project (Firenze, 3-5th July 2009). Along with tangible scientific advancement, it is important to recall the fruitful exchange of expertise, the promotion of tools sharing and the training of PhD and postdoctoral fellows that rendered this STREP project an example of successful European co-operation.



Elisabetta Cerbai PhD
Co-ordinator

NormaCOR
Centro Interuniversitario di Medicina Molecolare e Biofisica Applicata (CIMMBA)
Università degli Studi di Firenze
Viale G. Pieraccini 6
50139 Firenze
Italy

Tel: +39 0 554 271 247
Fax: +39 0 554 271 526

normacor@unifi.it
www.normacor.eu