CardioStemNet: Communique

Cellular and Molecular Targets to Promote Therapeutic Cardiac Regeneration

Paris (France), October 2014 – The CardioStemNet project (www.cardiostemnet.com), is a global scientific collaboration, financial supported by the Fondation Leducq through its Transnational Networks of Excellence in Cardiovascular Research programme. Coordinated by Dr David Sassoon (UPMC, Paris, France), and Dr Toren Finkel (NIH, Bethesda, USA) it has partners from San Diego (Mark Sussman), New York (Roger Hajar, Jason Kovacic), London (Nadia Rosenthal), Paris (Jean-Sebastian Hulot), Bad Neuheim (Thomas Braun) and Melbourne (Richard Harvey).

The project started in January 2014, and studies cardiac stem cell biology, cardiac de-differentiation, cardiac gene transfer and clinical heart disease to jointly address cellular and molecular processes contributing to cardiac repair. In the last 9 months, significant insights have already been obtained which have been reported in several major journal as original articles, and as strategic overviews via scientific reviews.

Below we report on three key issues that have been published by the project partners related to the fine control of the growing muscle and the environment in which the muscle cells are operating which provide novel perspectives for the development of effective corrective and restorative therapies.

Identification of critical molecular switches which regulate cardiac muscle growth and disease

Reported in the high impact journal, *Developmental Cell*, by the team of Thomas Braun, a molecular switch specific to cardiac and skeletal muscle has been identified. During the growth of any tissue, molecular control is regulated in part by the expression of specific and unique messenger RNA molecules. These unique molecules are called alternatively spliced transcripts and they contribute to why a heart cell is different from a liver cell, even though both the heart cell and the liver cell have the same DNA. While scientist have known about these alternatively splice transcripts for some time, very little is known regarding how they are generated. The Braun group has now identified the factor RBM24 as critically important in the generation of muscle-specific alternatively splice transcripts.

Their work demonstrates that RBM24 acts as an important muscle-specific molecular control for cardiac and skeletal muscle development. Several disease-relevant muscle-specific genes were regulated by this factor, which may provide future insights into the pathogenesis of cardiomyopathies and disorders of the basic units that form muscle fibres. The biological function of this factor strongly suggests that dysregulation of RBM24 may also be involved in a number of cardiac developmental abnormalities. As such, RBM24 appears to hold significant diagnostic and therapeutic potential.

Preclinical confirmation that heart function can be improved following gene therapy

Roger Hajjar's team from New York, are pioneers in cardiac gene therapy, aiming to restore heart function following myocardial infarction. Myocardial infarction is one of the major causes of heart failure.

It is characterized by poor perfusion, chronic loss of heart muscle cells (cardiomyocytes), scar formation, and adverse heart remodeling. Recently, cell therapy has received significant attention due to its potential for regenerating cardiomyocytes and replacing scar tissue with new cardiomyocytes. Despite the initial expectations that cardiac muscle regeneration would occur by introducing stem cells into the ischemic heart, most studies have failed to show a restoration of the functional tissue. Reported in the journal *Circulation*, Roger's team used the pig as a preclinical animal model and demonstrated that gene transfer of Stem Cell factor (SCF) at the ischemic border area improved heart systolic function up to 3 months post-treatment. These results advance the potential of SCF gene transfer as a future treatment option for ischemic heart failure. While longer term follow-ups are required to establish the full potential of SCF gene transfer as an efficacious approach to treat heart failure, the importance of the present study in pigs which have much closer physiological profiles to human hearts demonstrates that the functional improvement in a large animal study is a critical step in providing relevant information that will permit the translation of SCF therapy to clinical application in humans.

Relating regeneration to autoimmunity

The team of Nadia Rosenthal has been working extensively on regulation of cardiac regeneration by the immune system. Previous work by Nadia's team has shown that locally acting Insulin-like growth factor-1 (IGF-1) induced more complete repair in response to LAD ligation, resolving scar formation of injured hearts. An early decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines in IGF-1 treated hearts was observed, indicating that this growth factor drives regeneration in part by modulating the inflammatory response to pathological conditions. In their recent report, published in *Experimental and Molecular Medicine*, Nadia's team has now established that IGF-1 also plays a role in reduction of autoimmune disease. They established that IGF-1, already approved by the regulatory authorities for human use, reduces the autoimmune response and halts disease in mouse models of Type 1 diabetes and multiple sclerosis via the recruitment and local proliferation of T-regulatory cells in the target tissue. These cells counteract the imbalance of immune response, and their proliferative potential is impaired in human autoimmune disease.
The dual role played by IGF-1 in promoting regeneration and suppressing autoimmunity suggests that endogenous regenerative capacity (involving tissue stem or progenitor cells) and immune tolerance may be directly linked. IGF-1 can be used during a confined period of continuous systemic biotherapeutic delivery using a clinically relevant, accepted method for administering drugs in humans thereby representing a readily applicable therapeutic avenue for facilitating cardiac regenerationthrough the local and specific control of the immune system.

The work highlighted in this communique has been reported in:

Yang et al., RBM24 Is a Major Regulator of Muscle-Specific Alternative Splicing, Developmental Cell (2014), http:// dx.doi.org/10.1016/j.devcel.2014.08.025

Ishikawa et al, CIRCHEARTFAILURE.114.001711doi: 10.1161/CIRCHEARTFAILURE.114.001711, Stem Cell Factor Gene Transfer Improves Cardiac Function After Myocardial Infarction in Swine

Bilbao et al, Experimental and Molecular Medicine, Insulin-like growth factor-1 stimulates regulatory T cells and suppresses autoimmune disease 2014 (in press)

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About CardioStemNet

CardioStemNet is a project, supported through a grant from the Fondation Leducq, which brings together teams from San Diego, Washington, New York, London, Paris, Bad Neuheim and Melbourne in a global network of specialists, with cutting edge technological platforms to study cardiac stem cell biology, cardiac de-differentiation, cardiac gene transfer and clinical heart disease to jointly address cellular and molecular processes contributing to cardiac repair.

At present, no scientific consensus has emerged regarding what process regulates cardiac regeneration, and CardioStemNet will investigate these various hypotheses in a cooperative fashion to advance the field.

CardioStemNet focuses on 3 key questions:

1. To understand the biology of the various identified cardiac stem cell populations and comprehend what contribution each stem cell population makes under normal physiological conditions and after injury.

2. Address the fundamental constraints on the regenerative response. Evidence suggests that cardiac regeneration occurs in lower vertebrates (e.g. fish) and in the new-born heart in mammals. Nonetheless, this process is largely absent in the adult mammalian heart. Understanding how quiescence is maintained, what unique requirements exist and what signaling and pathways are activated will allow us to understand what limits the regenerative response after injury.

3. To use this knowledge for the development of rational therapeutic approaches to test methods to activate endogenous regeneration using small molecules or siRNA-directed therapies.