BIO_2

Title of the doctoral program

Bioengineering and Medical-Surgical sciences

Title of the research activity

Boosting cardiac regeneration: breakthrough in left ventricular assist device (VAD) and autologous stem cell combined therapy

Short description of the research activity

Left ventricular assist devices (LVADs) are commonly used as an effective treatment to support end-stage heart failure patients, either as bridges to transplantation, to recovery or as destination therapy. Once supported, patients have a partial or complete resolution of their heart failure state, improved survival to transplantation and enhanced quality of life and functional status. These mechanical pumps promote a complex of anatomic, functional, cellular, and molecular changes in the myocardium, processes that are known overall as “reverse remodeling”, leading to significant improvement of cardiac performance. In fact, whereas the use of VAD as a “bridge to recovery” has been successfully reported for acutely decompensated patients, which have reasonable likelihood of recovery with support, few adult patients with chronic long-standing heart failure will do well after this intervention, supporting the need of further clarifications on the pathophysiology of recovery. We also lack insights on markers that will predict meaningful recovery of the chronically injured myocardium. It is also possible that the high systemic infection rates and altered immunologic status associated with VAD insertion may be counter-regulatory, contributing to heart failure deterioration rather than cardiac "healing". Although poorly understood, in few patients, these changes are associated with partial or even complete myocardial recovery. Transient peripheral recruitment of CD34+ cells in VAD-treated patients has been documented and could probably represent a functional bone marrow response for mechanical circulatory support, presumably leading to biological processes that may accelerate the improvement of cardiac performance, including the activation of local progenitors, as part of their paracrine potential. The evaluation of the properties and the potential role played by resident progenitors in this process is required as a first strategic step to proceed forward with autologous cardiac cell therapy(aCCT)in these subjects. The unique opportunity of studying the structural and biological changes occurring in a human natural dynamic model of resting heart failure, as that provided by VAD-assisted patients, would open an important breakthrough both in the comprehension of the regenerative potential associated to remodeling/reverse remodeling processes and their important diagnostic-therapeutic applications (VAD-autologous cell combined therapy).It is possible that the therapeutic success of this device as a “bridge torecovery”,could be several folds amplified as a real healing therapeutic tool, once the right patients population (adult acute heart failure (cardiogenic shock)/chronic heart failure) and time-window sampling could be assessed. General aim of the project: in vitro/in vivo characterization and study of the pro-regenerative potential of VAD-assisted hearts and definition of their suitability/eligibility to undergo autologous cardiac cell therapy.To achieve this main goal, the following objectives will be pursued:

1. to determine the properties of CPCs (cardiac progenitors cells) grown as Cardiosphere and CDCs (cardiospheres derived cells) isolated from heart biopsies of patients with terminal HF before, during and after VAD treatment(when possible)

2. to define the best microenvironment where amplification and phenotype maintenance of CPCs is guaranteed, by focusing on the modifications of CPC proliferation and viability upon adhesion to different ECM substrates

3. to evaluate in vivo their efficacy and regenerative potential after injection in infarcted nude SCID mice

4. to assess the relationship between the individual patients CPCs regenerative/differentiative

potential with other multiple clinical and hemodynamic parameters

5. to correlate clinical outcomes of patients who underwent LVAD implantation with the regenerative potential of CPCs grown as Cardiosphere and CDCs isolated from "own heart biopsies" in an "in vivo" experimental model.

6. to create bioscaffolds that could be populated by CPCs and CDCs

Scientific responsible (name, surname, role, email)

Mauro Rinaldi, Principal investigator, mauro.rinaldi@unito.it

Number of vacancies for XXXI cycle (3 years program)

1

Specific requirements (experiences, skills)

Non required

Website of the research group (if any)

http://www.cittadellasalute.to.it/?option=com_content&view=article&id=176%253Acardiochirurgia-u&catid=57%253Asanitarie&Itemid=1