Original Article

Using Adult Stem Cells to Treat Heart Failure—Fact or Fiction?

Hendrik Zimmet, FRACP FCSANZ [a,b,*] and Henry Krum, PhD FRACP FCSANZ [a,b]

[a] *Monash Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology & Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia*
[b] *Department of Medicine, Monash University, Alfred Hospital, Melbourne, Australia*

Heart failure is a major health problem on a global scale. Current therapies include drug treatments, lifestyle modification, device therapy and heart transplantation. However, the "holy grail" of heart failure treatment would be to achieve widespread regeneration of diseased cardiac tissue. Examples of regeneration of living tissue are present in nature and involve stem cells. The two key defining properties of stem cells are their ability to renew themselves through cell division and to differentiate into various cell types. Generally, stem cells can be classified into embryonic or adult forms. Human adult stem cells are ethically appealing and have already been used in clinical trials in a variety of disease states. Bone marrow derived stem cells, skeletal myoblasts and resident adult cardiac stem cells are being explored as potential cell types for heart failure treatment. These cells can be delivered to the heart via a number of routes. Several clinical trials using adult stem cell have shown improvements in cardiac function, however, the mechanism of their action is unclear and widespread tissue regeneration is not evident. A more comprehensive understanding of regenerative physiology at the "benchside" combined with ongoing investigations at the bedside, will be paramount in achieving the ultimate goal of stem cell treatment—complete regeneration and repair of tissue.

(Heart, Lung and Circulation 2008;17S:S48–S54)

Keywords. Stem cells; Heart failure, Adult stem cells; Cell therapy; Tissue regeneration

The problem of heart failure

Heart failure is an increasing problem on a global scale. Harvard University School of Public Health projected figures indicate that between 1990 and 2020 there will be a shift in the nature of global burden of disease from communicable diseases, such as diarrhoeal disease, to non-communicable diseases such as ischaemic heart disease, type 2 diabetes and depression [1]. An increase in the incidence of heart failure will likely follow.

The prevalence of heart failure in Australia is not accurately known. However, it is estimated that at least 300,000 Australians are affected with 30,000 new cases being diagnosed each year [2]. In 1997, 41,000 hospital admissions in Australia were for heart failure [2]. These admissions were often re-admissions and typically longer stays that consequently resulted in higher than average hospital costs. The recent Canberra Heart Study has provided important new information on heart failure prevalence in Australia. It found the overall prevalence of clinical heart failure, in 2000 residents of southern Canberra, aged 60–85 years, to be around 6.3% (95% CI 5.0–7.0). Interestingly, of the patients found to have left ventricular systolic dysfunction, the majority (59%) were asymptomatic. Thus, patients with symptomatic heart failure represent the "tip of the iceberg" with regard to the national burden of heart failure [3].

Treatment of heart failure

Presently, heart failure treatments include drug treatments, lifestyle modification, device therapy and heart transplantation. The mainstay of drug treatment is angiotensin converting enzyme inhibitors (ACEI), beta-blockers and in certain circumstances aldosterone antagonists (e.g., spironolactone), diuretics and angiotensin receptor blockers (ARBs). Device therapies used in specific heart failure settings comprise cardiac resynchronization therapy (CRT), implantable cardiac defibrillators (ICD) and ventricular assist devices. Heart transplantation is utilized in selected patients whose heart failure is refractory to maximal pharmacological and device therapy. Improvements in heart failure care through drug and device treatment have resulted in less demand for heart transplantation. The "holy grail" of heart failure treatment, however, would be to achieve widespread regeneration of diseased cardiac tissue in place of diseased myocardium.

* Corresponding author at: Monash Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology & Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC 3004, Australia. Tel.: +61 3 9903 0569; fax: +61 3 9903 0556.
E-mail address: Hendrik.Zimmet@med.monash.edu.au (H. Zimmet).

1443-9506/04/$30.00
doi:10.1016/j.hlc.2008.09.006

Tissue regeneration is a reality

Regeneration is broadly defined as the ability to restore lost or damage tissues, organs or limbs. From a physiological viewpoint it involves the reactivation of developmental biological processes.

To begin with, it is important to emphasize that regeneration of complex biological structure is not science fiction. Such regeneration is seen and has been present in nature long before the field of modern medicine began. A starting point is to consider the salamander or axolotl which, following traumatic limb amputation, completely regrows a new limb with all constituent structures, the process taking 7–10 weeks [4]. The zebrafish provides us with an example of heart regeneration in nature. When its myocardium is injured, it regenerates all of the tissue components with no apparent scarring [5].

Greek mythological legend holds that Prometheus, the titan honored for stealing fire from Zeus and giving it to mortals, survived chained to a mountain top with eagles eating his liver day after day because it "grew back" [6]. Interestingly, the Greek word for the liver – *hêpar* – is thought to derive from the verb *hêpaomai*, which means repair [6]. In fact, in humans, the liver has a remarkable capacity to regenerate after injury. When over half of its volume is resected, new DNA synthesis is initiated within 12 h of injury and the liver will completely regenerate over the period of 2 weeks [7,8]. This ability of the human liver to regenerate has facilitated the current clinical practice of living-related donor liver transplantation [8].

Stem cell therapies—cell-based therapy and tissue engineering

There are two broad approaches to the use of stem cells in cardiovascular therapeutics.

The first approach, and the focus of this paper, is cell-based therapies. These entail the delivery of a volume or mass of cells to the tissue being targeted for treatment. The mode of delivery may be varied and is discussed further in a subsequent section of this paper (Section '*Modes of stem cell delivery to the heart*').

The second approach, tissue engineering, has been developed to create sheets of tissue and ultimately whole organs. Tissue engineering uses stem cells as building blocks or basic units to grow specific types of tissue. In creating an organ, several different stem cell populations may be required to create the different cell types that comprise that organ. Tissue engineering also uses scaffolding, analogous to the scaffolding of a building, to provide the structural framework for organ construction. In animal models, decellularized organs have produced fibrous organ scaffolds which are then subsequently seeded with stem cells [9]. To hold stem cells onto the scaffolds a "glue" providing an environment that simulates extracellular tissue matrix is required. Biomatrices using various structural proteins and nutrients have been developed for this purpose.

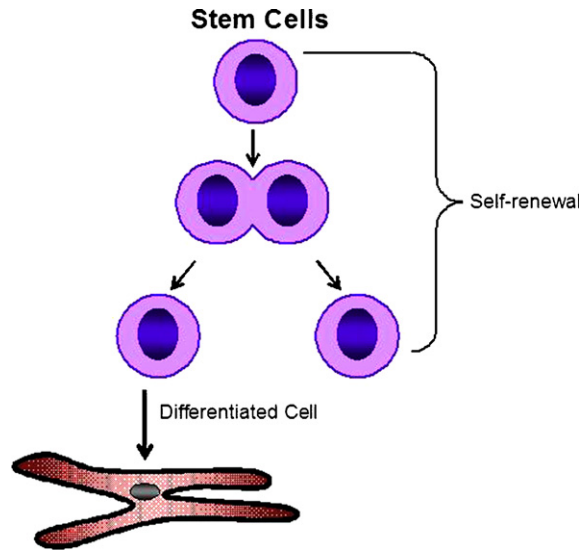

Fig. 1. *The two key defining properties of stem cells.*

What are stem cells?

The term "stem cell" arose from the concept that these cells have properties analogous to those of the stem of a plant. In plants, the stem may grow to produce more stem, that is, more of itself, or different structures such as leaves or flowers. This elegantly illustrates the two key properties that define stem cells. Firstly, they have the ability to renew themselves for long periods through cell division. Secondly, under specific conditions they can differentiate into a spectrum of different cell types (Fig. 1).

Stem cells have a hierarchy in terms of their ability to differentiate into other cell types. This ability is termed their differentiation "potential" (Fig. 2). In nature, the stem cell with the greatest ability to differentiate into various different cell types is the zygote—the first cell of human life, a sperm cell fused with an egg cell. This cell is termed

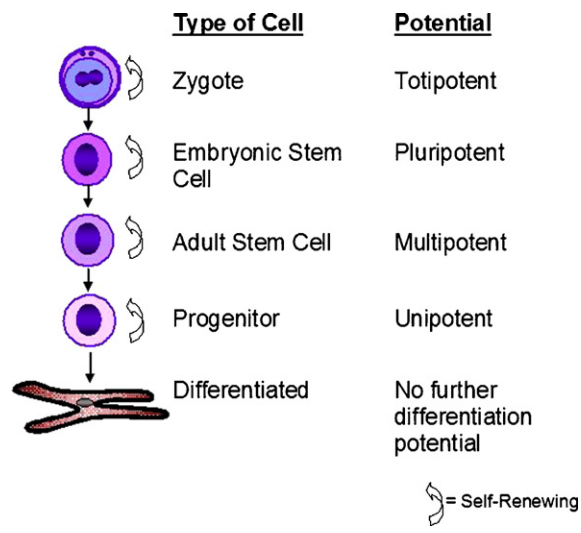

Fig. 2. *The hierarchy of stem cell potency.*