Different organs and tissues in the human body have very different capacities for natural repair following injury. However, there is for each organ or tissue an injury threshold beyond which its endogenous repair capacity becomes overwhelmed. This results in a loss of function that frequently worsens over time. Until recently, the only strategies available to address this problem have been directed at limiting the extent of injury by, for example, re-opening occluded vessels as quickly as possible to limit cell death from hypoxia, or limiting a chronic inflammatory or auto-immune response. Adult and embryonic stem cells have the potential to change this paradigm by creating treatments that regenerate and restore function in settings where this was not previously possible. This can be achieved in two, non-mutually exclusive ways: first, to use stem cells for the generation of cells that replace those lost to disease or injury; and second, to stimulate previously irreparable organs and tissue to heal themselves.

**Regeneration by Replacement**

Adult stem cells, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPS cells) are natural candidates for the replacement strategy as they possess the ability to generate large numbers of many different cell types. Adult stem cells have been shown to elicit a clinical benefit by boosting natural repair mechanisms rather than just generating replacement cells – putting them at the forefront of research into regenerative medical treatments.

**Keywords**

- Adult stem cells
- Regenerative medicine
- Adipose-derived stem cells

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By John Fraser at Cytori Therapeutics Inc

**Figure 1:** The Cytori Celution System
different kinds of functional cells. Indeed, the ability of ESCs and iPS cells to generate almost every type of cell in the body, combined with their essentially unlimited proliferative capacity, make them particularly strong candidates for this approach. By contrast, although repair and replacement is the natural function of adult stem cells, their ability to generate replacement cells appears to be largely restricted to only those cell types present within their tissue of origin. For example, adult stem cells within the breast are capable of generating different breast cell types but have limited, if any, capacity to form other tissues. The same appears to be true of stem cells present within the heart and central nervous system, although it is clear that the native repair capacity of these organs is very limited. Nonetheless, the clinical value of adult stem cells has been very clearly demonstrated in tens of thousands of bone marrow transplant procedures in which diseased or dysfunctional mature blood cells have been ablated and replaced with healthy cells generated by haematopoietic stem cells present within donor marrow.

Mesenchymal stem cells (MSCs) – bone marrow-derived stem cells that can generate bone and other connective tissue types – appear to be an exception to this rule as they can also form cells with characteristics of cells unrelated to the marrow, for example, nerve and heart tissue. However, while they acquire certain neuronal or myocardial tissue properties under particular artificial cell culture conditions, they have limited capacity to produce fully functional, terminally differentiated cells (1). For these reasons, it appears that the ability of adult stem cells to address overwhelming injury by simply generating replacement cells may be limited. By contrast, robust, reproducible generation of mature functional cells from ESCs is well established. Of course, it should be noted that ESCs and iPS cells have their own difficulties in terms of controlling their differentiation to avoid formation of the wrong tissue type or, in the extreme case, a teratoma or tumour (2). Just as importantly, it will be critical to develop appropriate delivery methods that would, for example, allow successful integration of ESC- or iPS cell-derived heart cells into the electrical circuitry of a patient’s heart in a way that avoids creation of a potentially lethal arrhythmia.

Indeed, by its nature, the replacement approach to regenerative medicine has proven extremely difficult to deliver beyond relatively simple tissues and structures. The enormous clinical success of bone marrow transplantation for inherited and malignant disease is due in very large part to the simplicity of the procedure. Following a simple intravenous infusion of the donor marrow cells, the biology of haematopoietic stem cells takes over as they home to the marrow cavity and begin the process of restoring haematopoietic function. It is far more difficult to recapitulate the complex developmental and regenerative mechanisms that allow functional integration with adjacent tissues and incorporation into host site vasculature, irrespective of whether the donor cell source is adult or embryonic stem cells. Thus, while this approach has enormous promise, it has to date been applied clinically in only a narrow range of disease states, all of which have used adult cell sources. These include regeneration of the mandible (3), creation of engineered bladders for patients with severe bladder disease (4) and repair of cartilage with cultured autologous chondrocytes (5).

Regeneration by Boosting Repair

The ability, however limited, of MSCs and their relatives to differentiate into heart cells led to the suggestion that these cells be applied in the treatment of heart disease. Indeed, preclinical studies in small and large animal models have clearly and reproducibly demonstrated benefit. However, a closer examination of these animals showed that this benefit occurred without any evidence that it was achieved by stem cells generating replacement cells and then Figure 2: Microscopic image of adipose tissue
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Successfully and safely integrating them into the injured tissue. Another advantage is that it appears to be effective in many different disease or injury settings. This may be due to the commonality of the wound healing process throughout the body. Thus, the repair model of regeneration has been applied clinically in acute and chronic myocardial ischaemia (7), cutaneous wound healing (8), limb ischaemia (9), tracheal repair (10), Crohn’s Disease (11) and breast reconstruction (12).

Preclinical proof-of-concept has been demonstrated in many other conditions including Parkinson’s disease, acute renal injury, pulmonary disease, osteoarthritis and Huntington’s disease. In these conditions, it appears that benefit is achieved by the ability of the regenerative cells to release growth factors that reduce cell death, minimise inflammation and scarring, and stimulate the tissue’s own stem cells and other repair mechanisms.

**Adipose Tissue-Derived Cells and Regenerative Medicine**

In 2001, Zuk et al demonstrated that human fat tissue contains cells that could be used in regenerative medicine (13). These cells – now referred to as adipose-derived stem cells (ADSCs) – could be grown and expanded in cell culture and were capable of differentiation along several lineages. Indeed, ADSCs share many properties with bone marrow MSCs and, consequently, share much of the potential of MSCs in both approaches to regenerative medicine. However, there are several differences. In terms of clinical application, the most significant difference is in the vastly greater number of stem cells present in fat tissue than in marrow. For example, the frequency of MSCs in the bone marrow of adult human is, on average, one stem cell per 200,000 cells (14). In contrast, the frequency of these cells in adult adipose tissue is of the order of 1 in 100 cells – two thousand times greater than in the marrow (15). This means that, while cell culture may be needed to generate a useful dose of MSCs from bone marrow, it may not be when using adipose tissue as a cell source. This has now been amply demonstrated in a number of published clinical reports using freshly-isolated, non-cultured cells from human adipose tissue in wound healing (8), fistula repair (10), calvarial bone repair (16), breast reconstruction (12) and urinary incontinence (17). Clinical data from prospective clinical trials has not yet been published but has been presented at international meetings – including data from randomised, double blind studies of chronic myocardial ischaemia (18) and acute myocardial ischaemia (19), and from a single arm study of breast reconstruction (20). Clearly fat tissue is not like bone marrow and cannot be simply infused into the blood vessels without appropriate processing. Further, clinical use demands that tissue processing meets recognised standards of reproducibility and sterility. The Celution® System was developed by Cytori with exactly these criteria in mind. This CE-marked device is used today to replace, repair, reconstruct or augment surgical soft tissue defects, liposuction defects, congenital asymmetry, anatomically deficient soft tissues and soft tissue wasting disorders, as well as for general surgery procedures to facilitate healing in rectal and vaginal fistulae in Crohn’s disease. The Celution System has been used in several of the clinical trials and studies listed above, including two randomised, double blind, placebo-controlled studies for heart disease (one for heart attack (19), the other for chronic heart disease (18)), a 71-patient single arm study in breast reconstruction (20), and smaller case series studies in stress urinary incontinence (17) and wound healing (8). Several other clinical studies are underway in a variety of clinical applications around the world.
Conclusion
Degenerative conditions arise when a tissue or organ sustains an injury that overwhelms its ability to repair itself. New strategies are being developed that bring about regeneration of function, even in the face of overwhelming injury, by delivering cells to replace those lost to the injury or by boosting natural repair mechanisms. Repair and replacement is the natural function of adult stem and regenerative cells. Consequently, these cells are at the vanguard of innovative approaches and devices in pilot studies and, increasingly, in rigorous, controlled clinical trials.

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John Fraser is Principal Scientist at Cytori Therapeutics Inc, a US-headquartered company engaged in commercialisation of medical technologies enabling the use of adult stem and regenerative cells from human adipose tissue for clinical benefit. He has more than 25 years of experience working with adult stem cells. Prior to joining Cytori, John was an Associate Professor in the Department of Medicine at the University of California at Los Angeles (UCLA), working within the bone marrow stem cell transplant programme. He has a PhD from the University of Otago (New Zealand) and has published more than 40 peer-reviewed papers.

Email: jfraser@cytori.com