

The Regenerative Potential of Stem Cells

The European Commission defines Regenerative Medicine as “the possibility of replacing degenerated or damaged tissue, and thereby curing numerous diseases that are currently intractable.”¹ This definition includes two distinct approaches: (1) implantation of tissues and organs grown in the laboratory when the body cannot heal itself and (2) the stimulation of previously irreparable organs and tissues to heal themselves.

The first approach is based upon the concept of *replacement*, in which regenerative cells or their progeny replace functional cells lost to injury or disease. In particular, this approach encompasses the concept of tissue engineering in which living cells are loaded onto a scaffold and grown under conditions that promote the population of that scaffold with functional cells and, ultimately, tissue. While this approach has enormous promise, it has to date been applied clinically in only a narrow range of conditions. These include regeneration of the mandible², creation of engineered bladders for patients with severe bladder disease³, and repair of cartilage with cultured autologous chondrocytes⁴.

The second approach to regenerative medicine is based on the concept of *repair*. In this approach, the regenerative cells are not delivered to replace injured cells directly but rather to stimulate natural repair mechanisms. This is based on the fact that, in many disease or injury states, the natural repair capacity of the tissue or organ is either overwhelmed by the extent of injury or has become exhausted over time. Examples of this include loss of contractile tissue following a heart attack

and impaired healing in chronic wounds. In this context, regenerative cells delivered to the injury or wound act to boost the ability of local repair mechanisms to maintain or restore function. For example, they may stimulate proliferation of local tissue stem and progenitor cells, increase migration or mobilization of cells involved in healing, or reduce ongoing loss of parenchymal cells to inflammatory or apoptotic processes. In essence, regenerative medicine in this context is applied to create an improved environment for healing. In practice, this is much easier to achieve than generating replacement cells *de novo*. The surprising fact is that several regenerative strategies that were originally designed to provide benefit through the replacement mechanism were subsequently found to act through stimulation of repair.

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 kinds of functional cells. The totipotency of ESCs and iPS cells combined with their essentially unlimited proliferative capacity make them particularly strong candidates in this approach.

Adult stem cells are more restricted in their ability to generate fully differentiated, functional progeny. That is, while they are often robust generators of cell types present within the tissue of origin, their ability to generate cells outside that tissue is less efficient. For example, mesenchymal stem cells (MSCs) are a bone marrow-derived

population with robust ability to generate bone and other connective tissue types⁵. However, while MSCs have also been shown to be capable of differentiating into neuronal and myocardial cells *in vitro*, this capacity is much less robust than that for osteogenic differentiation. Only a fraction of the MSCs exhibit markers of induced differentiation with very limited, if any, production of fully functional, terminally differentiated nerve cells or cardiac myocytes^{6,7}. By contrast, generation of mature functional neuronal and cardiac cells from ESCs is well-established⁸⁻¹⁰. On this basis it appears that adult stem cells may be a poor choice for patients with end stage cardiac disease where benefit can only be achieved by delivery of increased contractile tissue. However, this may be a function of the state of the art rather than a reflection of inherent limitations in stem cell biology. That is, it may be that improved understanding of adult stem cells will lead to generation of efficient *in vitro* differentiation protocols. Of course, in this setting ESCs and iPS cells have their own difficulties in terms of controlling differentiation and, just as importantly, successfully integrating ESC- or iPS cell-derived contractile tissue into the electrical circuitry of the recipient heart.

Indeed, by its nature the replacement approach to regenerative medicine has proven extremely hard to deliver beyond relatively simple tissues and structures. Experience has shown that it is very difficult to recapitulate *in vitro* the complex developmental and regenerative mechanisms that allow incorporation of an engineered tissue into host site vasculature

as well as functional integration with adjacent tissues.

REGENERATION BY BOOSTING REPAIR

The ability, however limited, of MSCs to differentiate into cardiac myocytes led to the suggestion that these cells be applied in the treatment of cardiac injury. However, while preclinical studies clearly demonstrated benefit, a closer examination showed that this benefit was derived without retention of the stem cells or their progeny. That is, the number of donor-derived cells remaining in the myocardium was, by a very large margin, insufficient to account for the observed benefit. In other injury models with MSCs and other regenerative cell types, benefit has been demonstrated without long-term retention of the cells or their progeny or provided too soon after treatment for it to be derived by replacement phenomena.

For example, several cell types are capable of providing substantial benefit within the first few days following acute renal injury and in the absence of evidence for donor cell retention in the kidney¹¹⁻¹³. Further, one study has demonstrated that this benefit can be obtained by repeated administration of medium in which the regenerative cells were cultured suggesting that the benefit is derived by paracrine or endocrine expression of growth factors¹³. This paracrine model is increasingly being recognized as an important means by which regenerative cells provide benefit¹⁴. It is, however, a difficult model to dissect inasmuch as regenerative cells, as living entities, respond to their surroundings and, hence, change the growth factors they express as their environment changes. For this reason it is very difficult to ascribe benefit to a single factor or even a single effector mechanism. Benefit can be derived through multiple mechanisms including modulation of inflammation and/or fibrosis^{15,16}, stimulation of angiogenesis^{17,18}, inhibition of apoptosis^{19,20}, enhancement

of recruitment of native tissue stem and progenitor cells^{21,22}, and stimulation of proliferation of local effector cells¹¹.

Another advantage of this approach is that it appears to be effective in so many different disease or injury settings. This may be due to the commonality of the wound healing process throughout the body.

Wound healing is a complex process that occurs through a series of overlapping phases: (1) Hemostasis, (2) Inflammation, (3) Proliferation, and (4) Remodeling. While the precise timing of these phases differs between injury types, the general progression through these phases and the cytokines and other mediators that accompany this process is generally constant. For this reason, strategies that improve regeneration by reducing fibrosis (within the remodeling phase) or enhancing angiogenesis (part of the proliferation phase) in one disease state may also improve it in another organ or tissue.

Thus, the repair model of regeneration has been applied clinically in acute and chronic myocardial ischemia²³, cutaneous wound healing^{24,25}, limb ischemia²⁶, tracheal repair²⁷, multiple sclerosis²⁸, stroke²⁹, spinal cord injury^{30,31}, liver disease³², Crohn's Disease³³, and breast reconstruction³⁴. Preclinical proof-of-concept has been demonstrated in Parkinson's Disease³⁵, acute renal injury¹¹, pulmonary disease³⁶, osteoarthritis³⁷, and Huntington's Disease³⁸.

ADIPOSE TISSUE-DERIVED CELLS AND REGENERATIVE MEDICINE

In 2001, a research team at University of California, Los Angeles, US, led at the time by Marc Hedrick M.D., President of Cytori, demonstrated that human adipose tissue contains cells that could be used in regenerative medicine³⁹. 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 lineages⁴⁰.

Since this initial description ADSCs have been shown to be capable of differentiating into a surprisingly broad range of cell types including bone⁴¹, cartilage³⁹, skeletal muscle⁴², smooth muscle⁴³, cardiac muscle⁴⁴, nerve cells⁴⁵, oligodendrocytes⁴⁶, hepatocytes⁴⁷, and pancreatic beta cells⁴⁸. 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. Cell culture is used in the production of ADSCs following the paradigm established MSCs^{49,50}. However, there is an enormous difference between the cell populations used to initiate cultures of MSCs and those of ADSCs. Specifically, the stem cell frequency in the bone marrow of adult humans is on the order of one stem cell per 200,000 total nucleated cells⁵¹. Cell culture is, therefore, necessary to enrich these cells and expand the number available to a clinically adequate cell dose. By contrast, the frequency of these cells in digested adipose tissue is on the order of one in 100 nucleated cells^{52,53}; 2,000 times greater than marrow. Further, the process of cell culture needed to expand the stem cell fraction changes properties of the cells present and results in elimination of other cell types with demonstrated utility⁵⁴. These differences suggest that the cell culture required to expand stem cells from marrow may not be necessary, and may even be disadvantageous, when using adipose tissue as a stem cell source.

Clinical use of cultured cells requires the application of robust and stringent Good Manufacturing Practices (GMP) to ensure sample identity and to control the risk of contamination with infectious or potentially tumorigenic material or even culture induced oncogenic transformation. Culture-mediated expansion of a sufficient cell dose can also be time consuming and potentially delay treatment. For these reasons, use of freshly-isolated, non-cultured cells have enormous practical

advantages over cultured cells, particularly in the autologous setting.

This, of course, begs the question: do freshly-isolated cells provide regenerative benefit? Data from numerous clinical case reports and studies show that this is the case. Clinical case report data with freshly-isolated Adipose-Derived Regenerative Cells (ADRCs) have been published in wound healing²⁵, fistula repair²⁷, calvarial bone repair⁵⁵, breast reconstruction³⁴, and urinary incontinence⁵⁶. Additional clinical data from larger clinical trials has not yet been published but have been presented at international meetings including data from randomized, double blind studies of chronic myocardial ischemia⁵⁷ and acute myocardial ischemia⁵⁸, as well as from a single arm study of breast reconstruction⁵⁹.

ISSUES ASSOCIATED WITH CLINICAL USE OF CELLS FROM ADIPOSE TISSUE

Adipose tissue is a solid organ rather than a suspension of single cells like marrow or blood. Consequently, cells from adipose tissue must be obtained by enzymatic digestion. This requires application of clinical grade enzymes and reagents within a tissue processing method that minimizes the risk of contamination of the cells during processing. In addition, the methods applied must be validated to ensure that the amount of enzyme remaining with the cells after processing is safe for the intended route of administration. For approaches that deliver cells into the vasculature where enzyme is rapidly diluted by blood, the residual level that is determined to be safe may be considerably higher than the level that is safe for intramuscular delivery. Similarly, levels of post-processing cell aggregates and fragments of extracellular matrix that are safe for intramuscular delivery may not be safe for intravascular delivery.

What these concerns come down to is that the processing of adipose tissue to generate a population of regenerative cells for clinical use must be performed

within the context of GMP. This requires detailed standard operating procedures, certification of reagents, validation studies, and so forth. Alternatively, the Clinician-Scientist may use the Celution® System, a device for which these parameters have been developed, optimized, and validated by Cytori Therapeutics, Inc. This places the burden of GMP-compliance for ADRC processing on the device rather than on the user.

The Celution System is the only device currently available that automates and standardizes the extraction of adipose derived stem and regenerative cells. Clinical protocols have been developed by Cytori for safe tissue collection and cell administration in patients with various disease states.

The Celution System has been used in several of the clinical trials and studies listed above including two randomized, double blind, placebo-controlled studies for heart disease (one for heart attack⁵⁸, the other for chronic heart disease⁵⁷), a 71 patient single arm study in breast reconstruction⁵⁹, and smaller case series studies in stress urinary incontinence⁵⁶ and wound healing²⁵. Several other clinical studies are underway in a variety of clinical applications around the world. The Celution System is the only device with this kind of pedigree. In the course of developing Celution and performing the preclinical studies needed to initiate clinical trials, Cytori has amassed unmatched expertise with ADRCs, measurement of residual levels of processing enzymes, reproducibility of processing and development of parameters for safe tissue collection cell administration in patients with different disease states. This expertise has been built into the system.

SUMMARY

Regenerative medicine is an extremely promising avenue for the treatment of many diseases, injuries, and conditions that are inadequately addressed by existing modalities. The key building blocks of this

strategy are living cells derived from adult or embryonic stem cells or from induced pluripotent stem cells. These cell types have distinct biologic strengths and weaknesses and provide distinct risk: benefit considerations in different disease states. The broadest and most easily accessible opportunity appears to be in harnessing the ability of regenerative cells to boost natural repair mechanisms. In this context, adult stem cells have a clear advantage in terms of their ability to be used autologously, thereby eliminating issues associated with infection, rejection, or teratoma formation. The further ability to use adipose tissue as a source of regenerative cells that can be delivered in large amounts without the need for cell culture creates a novel opportunity for bedside application of regenerative medicine using the patient's own cells. The promise of this approach is already being realized in numerous clinical settings. The next steps will be the confirmation of this promise in rigorous, controlled clinical studies and the performance of pilot studies in novel areas.

About Cytori

Cytori is a leader in providing patients and physicians around the world with medical technologies that harness the potential of ADRCs from adipose tissue. The Celution System family of medical devices and instruments is being sold into the European and Asian plastic and reconstructive surgery markets but is not yet available in the US. www.cytori.com

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