Insights in Stem Cells

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Stem Cell Research 2017-Laboratory Training Guidelines for Clinicians Undertaking Stem Cell Therapy- Rachel Shparberg- University of Sydney

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Introduction

Stem cell therapy is becoming more frequent in many countries. Several issues regarding their use attracts both support and criticism from the various stakeholders, namely the public, treating clinicians, scientists, government agencies and commercial organisations. It is imperative that science establishes, at the minimum, validated methods that are reproducible to provide a framework for safety and efficacy. Once scientists have developed and published methods, it is again imperative that the treating clinician has a sufficient knowledge of the scientific terms, equipment and interdisciplinary approaches (Figure 1) used for stem cell treatments. Most clinicians have basic core university teaching in the fields of biology, chemistry and their interdisciplinary areas. However, specific awareness and understanding of stem cells is very limited for doctors, dentists and allied health practitioners. The authors have collaborated in clinical stem cell treatments with an emphasis on peer reviewed evidence-based scientific methods and clinical outcomes to establish patient inclusion/exclusion criteria. RS is a developmental cell biologist and has completed a doctorate in embryonic stem cells methodologies. ERV is an oral and maxillofacial surgeon who completed training in embryonic stem cell lines and subsequently published the first clinical stem cell study demonstrating safety and efficacy of autologous mesenchymal stem cells in humans when injected into the head, face and oral cavity to treat neuropathic pain. NB is a counsellor with a special focus on psychological issues of stress, anxiety and depression and how it impacts patients undergoing stem cell treatment. Taken together, the authors have a combined 20+ years of experience in laboratory cell biology, stem cell culture techniques, and clinical and psychological assessments. In addition, the combined experience of the authors when they have presented lectures for university students, postgraduate medical and dental clinicians, and the public has led to many frequent questions on topics such as safety, quality assurance and laboratory methods. Government agencies, insurance and professional indemnity companies rely on evidence to make monetary decisions that largely permit, or do not permit, use of stem cells. The purpose of this article is to provide the scientific framework of knowledge for clinicians to fulfil these obligations in the therapeutic use of stem cells.

Types of Stem Cells: A stem cell, by definition, is a cell that is capable of self-renewal over multiple cell divisions, maintains a normal karyotype and retains the capacity to differentiate into a variety of cell types, depending on the stem cell's level of potency. Three main classes of stem cells exist: Embryonic, Adult and Induced Pluripotent stem cells, each of which serves important laboratory and/or clinical purposes.

Embryonic stem cells: Embryonic stem cells (ESCs) are those that are derived from the blastocyst-stage embryo. The blastocyst contains a population of cells known as the inner cell mass (ICM) that will eventually give rise to the >200 specialised cell types that make up the foetus and adult (Figure 2). These ICM cells can be isolated from the blastocyst and when cultured in vitro can be maintained as pluripotent ESCs. When the culture conditions are such that ESCs are permitted to differentiate, they will do so spontaneously and randomly into cells that constitute the three definitive germ layers (ectoderm, mesoderm and endoderm) of the embryo proper

Adult stem cells: A focus on MSCs Adult stem cells are those which are derived from developed organs and are named usually by their tissue of origin, for example, neural stem cells. These cells are found endogenously in specialised 'stem cell niches' within the foetal and adult body and serve to repair and rejuvenate damaged and/or aging tissue. Unlike ESCs, adult stem cells are multipotent which means that they

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can differentiate into multiple cell types but are conventionally restricted to the cell types within their lineage of developmental origin. These stem cells are currently at the forefront of autologous regenerative cell therapies, with mesenchymal stem cells (MSCs) currently being the most widely investigated stem cell type for such therapies. MSCs are found throughout the body (including but not limited to bone marrow, adipose tissue, dental tissue, salivary glands and peripheral blood) [10-13], making them a relatively easy-to-obtain source of stem cells. MSCs have been shown to differentiate into a range of mesoderm-derived tissues including bone, muscle and adipose tissue, as well as transdifferentiate into ectoderm- and endoderm-derived cell types [11,14,15]. Importantly, MSCs secrete immunomodulatory factors such as cytokines and growth factors [16,17] that have been shown to aid in the immune response. Evidence also suggests that these factors may modulate the body's own stem cells to differentiate and repair damaged tissue [18,19]. Importantly, MSCs express cluster of differentiation (CD) molecules CD73, CD90 and CD105, but lack haematopoietic markers CD45 and CD39 [16], and express low levels of Major Histocompatibility Complex (MHC) I and MHC II. These properties prevent MSCs from inducing an immune response making them an attractive source of stem cells for autologous and allogeneic (cells from a foreign donor) cell therapy.

Stem Cell Maintenance and Differentiation: Stem cells are characterised by their ability to self-renew over extended periods of time in culture but are poised for differentiation when conditions are favourable. As such, the culture conditions in which the cells are grown in are vital for producing the appropriate cell population, be it stem cell maintenance or differentiation. General maintenance requires cells to be anchored onto the tissue culture plate allowing cells to attach and proliferate over time (Figure 4). As to prevent over-confluency and cell toxicity, cells must be sub-cultured to remove waste product from the medium, preventing a drop in pH, and to replenish nutrient supply to maintain optimal proliferation and growth (Figure 4). When ~70% confluence is reached, i.e., 70% of the surface of the plate contains viable cells, cells are dislodged (usually by enzymatic cleavage of surface proteins) and re-seeded on a newly prepared plate for continuous maintenance or for differentiation experiments.

Conclusion: Stem cells have gained much attention over recent years for their unique potential to assist in the regeneration of aging, diseased and dysfunctional tissue. In order for stem cell therapies to be administered as approved treatments, scientists and medical practitioners must have a basic scientific understanding of what stem cells are and how they communicate with each other and their environment in order to provide patients with the safest and most effective treatment possible. Underlying most, if not all medical interventions is the laboratory testing that occurs behind the scenes to validate and ensure that a therapy gives a high level of confidence for the clinician and patient. Stem cell therapy should not be exempt from these expectations. Government and professional health organisations acknowledge there is raised public awareness for optimal patient care and prevention of treatment risks and complications. It is well recognised that preventive mechanisms for comprehensive care includes ongoing mandatory professional education and training when undertaking new technologies. Balancing public demands for quick access to stem cell therapy can be achieved with knowledge, training and continued research.

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