Stem Cell Therapies for the Treatment of Neurodegenerative Disease

Stem cell therapies using adult stem cells taken from a patient's own bone marrow offer the possibility of curing the underlying pathology of neurodegenerative disease, rather than simply treating symptoms.

Studies on animals and humans document an expanding repertoire of multi-potent embryonic and adult stem cells that are able to differentiate to a multitude of derivatives crossing lineage barriers and adopting gene expression profiles of cells specific to other tissue-types. This flexibility is termed 'plasticity'. The plasticity of stem cells has brought them to the frontier of scientific research, the general idea being that their unique attributes could be harnessed to curative goals such as regenerative and protective applications for incurable diseases.

The ideal cells for application in cell therapy would have to possess several key properties. First, the safety for each application would have to be well-established, and animal product-free processes would be essential for such purposes. Second, the cell population would have to be highly expandable, allowing optimal utilisation of donor material. Third, the cells would need to have wide differentiation potentials, allowing differentiation into appropriate cell types for each application.

STEM CELL TYPES

The most primitive of all stem cell populations – offering the widest differentiation potential as well as a great capacity for self renewal – are embryonic stem cells (ESCs), obtained from the inner cell mass of developing blastocysts. ESCs are pluripotent stem cells that can give rise to cells of the three germ layers found in the embryo, but not to embryonic components of the trophoblast and placenta. Advances in the understanding of embryology and neurogenesis have helped ESC researchers to develop protocols which generate neural progenitors capable of differentiating into neurons, astrocytes and oligodendrocytes from human ESCs (1). Application of the embryonic pluripotent stem cells to clinical studies have been hindered by a number of factors: potential immune rejection in allogeneic transplantation, formation of teratomas, difficulty in obtaining donor tissue, and serious ethical and political issues (2).

Adult stem cells, on the other hand, can be easily obtained from various tissues of the adult human body including bone marrow, adipose tissue, skin, muscle and other visceral organs. Perhaps the most studied and best-known adult stem cell is the haematopoietic stem cell (HSC). Residing in the bone marrow, HSCs have long been known for their ability to differentiate along the blood system hierarchy. For more than 30 years, HSC transplantations have been used to replenish the blood system of patients suffering from haematological malignancies after immunologic irradiation. The different types of multipotent adult stem cells display the plasticity initially thought to be reserved exclusively for ESCs.

Accelerating research on adult stem cells is showing great promise, especially when a few major considerations are taken into account. First, the use of ESCs and foetal tissue raises major ethical dilemmas in many areas of the world, whereas adult stem cells can be easily obtained from adult donors, avoiding the ethical drawbacks. Second, implanting ESCs involves allograft transplantation, risking graft rejection, while the use of adult stem cells enables autologous stem cell transplantation. Third, adult stem cells pose little risk of teratoma formation (3).

MULTIPOTENT MESENCHYMAL STROMAL CELLS

Bone marrow-derived multipotent mesenchymal stromal cells (MSCs) provide the structural and functional support necessary for the generation of blood cell lineages from HSCs. Thus, MSCs were traditionally viewed as haematopoietic support cells, and were used mainly as feeder layers to culture HSCs in vitro. However, since the 1970s, extensive research on the properties of MSCs has yielded a vast amount of information about their unique multipotent characteristics, and focus has shifted to the study of this unique and rare cell type. MSCs are isolated from whole bone marrow by utilising their unique plastic-adherence properties. Plastic-adherent MSCs represent a unique heterogeneous population of stem and multipotent mesenchymal progenitor cells that are able to differentiate into several types of cell including osteoblasts, adipocytes, chondrocytes and myoblasts. These cells are characterised by expression of a distinct set of mesenchymal cell surface markers (CD105, CD73 and CD90), and a lack of haematopoietic markers (CD45, CD34, CD14 and CD19) (4).
Recent studies have shown that the differentiation potential of MSCs is not limited to mesenchymal derivatives. When cultured in vitro in mediums with various combinations of cytokines, growth factors, and other signalling molecules, Macs develop gene-expression profiles that are characteristic of muscle cells, bone cells, fat cells, epithelial cells, and endothelial cells and neural or glial cells. This supports the concept that bone marrow mesenchymal cells show a phenotypic potential of multi-lineage differentiation capacity. Additional studies found that MSCs – transplanted into different animal models – differentiated in vivo after transplantation into neurons, astrocytes and myelinating Schwann-like cells and oligodendrocytes. The pluripotency of MSCs has recently been attributed to their wide plasticity, whereby they express a range of genes in a non-specific manner and, upon signals from the environment (such as changes in the in vitro culture conditions), up-regulate certain genes while down-regulating others – resulting in a differentiated cell of a specific lineage (6). Together, these findings support the concept that MSCs provide a source of cells that could be used as a potent therapeutic tool for brain repair.

NEURODEGENERATIVE DISEASES

Neurodegeneration is a process of neuronal loss of function followed by neuronal cell death that is the common denominator of many neurological conditions. While the definition is broad, each neurological disease is typically caused by dysfunction or loss of specific cell types. Understanding the basis of the selective vulnerability that characterises neurodegenerative diseases could refine therapeutic approaches in which transplanted stem cells could replace a lost neuronal subtype or function.

In Parkinson’s disease, whether sporadic or inherited, dopaminergic neurons of the substantia nigra pars compacta (A9) progressively degenerate. Interestingly, other dopaminergic populations are relatively spared, including the adjacent ventral tegmental area (VTA or A10) neurons (7).

In Alzheimer’s disease, the earliest and the most consistent degeneration occurs in the forebrain cholinergic projection system, particularly in a structure called the substantia nigra of Meynert. West et al, 1994, showed that although neuronal and synaptic loss occurs diffusely across the brain, neurons in layer II of the entorhinal cortex and hippocampal CA1 neurons are particularly vulnerable (8).

Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig’s disease) involves the loss of upper and lower motor neurons; however, in ALS, motor neurons do not display universal vulnerability. Some motor nuclei (III, IV, VI and Onuf’s nucleus) remain relatively intact during terminal stages of the disease, while others (V, VII, XII and most of the spinal nuclei) usually degenerate (9).

Multiple sclerosis (MS) – the most common demyelinating disease of the central nervous system (CNS) in young adults – is an autoimmune disease encompassing both inflammatory and degenerative features that result in myelin degradation and eventually cause axonal loss (10). It is believed that these processes play a central role in disease initiation and progression. The destruction of the myelin sheaths and death of the myelinating oligodendrocytes result in demyelinated plaques, usually located in the vicinity of the optic nerve, the white matter surrounding the lateral ventricles, the cerebellum and the spinal cord.

PIONEERING STEM CELL THERAPY

Patients afflicted with neuronal damage, neurodegenerative disorders, spinal cord injury or stroke suffer the consequences of insufficient neurogenesis and cell renewal in their affected nervous system. Current therapies for the most part target symptoms, effecting a reduced frequency or severity of symptoms, but – ultimately – they are not able to halt the disease or deterioration of patients. The need for a therapeutic solution to the neuronal degeneration itself is pressing.

At BrainStorm Cell Therapeutics, Inc, we are pioneering research and development in adult bone marrow-derived stem cell therapy, aimed at treating these debilitating diseases. The company’s scientific team and business managers have chosen to focus their first commercialisation efforts on combating Parkinson’s and ALS diseases. The core technology, NurOwn™, is based on the breakthrough scientific achievements of Professor Eldad Melamed and Dr Daniel Offen at Tel-Aviv University.

The research team was among the first to successfully achieve the in vitro differentiation of adult bone marrow cells (animal and human) into characteristic neuron-like cells capable of releasing dopamine, and astrocyte-like cells capable of releasing several neurotrophic factors, including glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and others. To stimulate the differentiation of adult bone marrow stem cells into neurotrophic factor-producing cells, the cells were cultured in a medium composed of a unique combination of cytokines and growth factors. The neurotrophic factors produced by the differentiated cells have known neuroprotective qualities. The ability to induce differentiation into neurotrophic factor-producing cells by...
a process free of animal products makes the NurOwn™ technology highly attractive for treating other neurodegenerative diseases (such as ALS and multiple sclerosis) by autologous transplantation. Following promising results in animal models, we are currently engaging in large-scale preclinical studies to evaluate the effect of the NurOwn™ therapy on animal models of Parkinson’s disease and ALS.

The cell-therapy product that BrainStorm is developing benefits from the following advantages, making it a natural choice for near-future stem cell treatment. First, it is free of embryonic stem cells and is thus not subject to the ethical, religious and political controversy surrounding the use of these specific stem cells. Second, autologous bone marrow-derived stem cells offer particular benefits. They can form many different cell types, are relatively easy to harvest and do not present the risk of rejection as they are harvested from the patient’s own body. They also carry a minimal risk of forming tumours, whereas embryonic stem cells have a very high risk, and are able to capitalise on the 40-year safety record of bone marrow transplants.

The tireless efforts and exciting advances being made in developing new technologies utilising stem cells for the regenerative treatment of some of the most debilitating neurodegenerative diseases finally raise the possibility of offering patients and doctors hope for a cure in our lifetime.

References
2. Perin EC, Geng YJ and Willerson JT, Adult stem cell therapy in perspective, Circulation, 107, pp935-938, 2003
3. Fujikawa T, Oh SH, Pi L et al, Teratoma Formation Leads to Failure of Treatment for Type I Diabetes Using Embryonic Stem Cell-Derived Insulin-Producing Cells, Am J Pathol, 166, pp1,781-1,791, 2005
5. Suzukia H, Taguchia T, Tanakaa H et al, Neurospheres induced from bone marrow stromal cells are multipotent for differentiation into neuron, astrocyte and oligodendrocyte phenotypes, Biochem and Biophys Res Commun, 322, pp918-922, 2004