

ISSUES IN MEDICINE

Stem cells – 13 years since their isolation, is there any proven benefit to the patient?

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Stem cells are seen as the 'magic bullet'; while this may be true, their efficacy and safety in patients has not yet been established unequivocally. This article summarises the different types of stem cells and gives an overview of their

advantages and disadvantages, their use, and potential uses in the patient setting.

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Human embryonic stem (ES) cells were first isolated from the human embryo in 1998, sparking the hotly debated, controversial field of stem cell research. The controversy arose as these cells can only be derived from fertilised human embryos at the blastocyst stage, resulting in destruction of the embryo. Like the cells of the early embryo, ES cells can differentiate into any cell type or tissue – a property termed pluripotency. They are therefore seen by many as the 'magic bullet' because they have the potential to regenerate cells, tissues or organs to treat disease.

In consequence of the ethical difficulties of obtaining fertilised human eggs, numerous ES cell lines have been created. The primary cells for these lines were obtained from surplus IVF embryos with full, informed consent. They have since been perpetuated in sterile culture and are commercially available. Basic research has proven their ability to differentiate into a multitude of cell types. Legislation is struggling to keep pace with ES cell research, which has been hampered by ethical and political pressure, predominantly in countries with some form of stem cell legislation.

Google 'stem cell therapy' and you will be confronted with a plethora of companies across the world offering to cure disease. The vast majority of these companies – most exist in countries with limited or no regulation on stem cell use – claim to cure disease simply via injection of the cells. There are only anecdotal data, and no hard scientific evidence, to substantiate their claims. Stem cells are mitotically hyperactive and have been shown to form teratomas following injection into mice – a property that has ultimately led to the death of some patients hoping for a miracle cure.¹

Since the isolation of human ES cells, 2 less controversial stem cell types have been discovered: adult stem (AS) cells and induced pluripotent stem (iPS) cells. AS cells are not embryo-derived, but rather found within the tissues of the juvenile and adult body. Unlike ES cells, AS cell potency is restricted to a particular lineage, and is termed multipotency, e.g. lung AS cells are able to develop into several lung cell types, but not into other cell types. AS cells are few in number and, while some are relatively easy to harvest – such as those residing in the bone marrow, blood, skin, umbilical cord and muscle – those found in the brain or heart, for example, are difficult to obtain.

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In 2006, scientists demonstrated a major breakthrough in stem cell research: they could re-programme normal somatic cells to a pluripotent ES-like state by introducing – very surprisingly – just a handful of re-programming genes. These cells (iPS cells) have enormous potential: they have been shown to differentiate into many different cell types,² while obviating the ethical and harvesting drawbacks of ES and AS cells respectively. While the discovery of iPS cells is exciting, these are early days and there are no registered trials using these cells in patients. The safety of their use has not been proven unequivocally and there are concerns that these 'old' re-programmed somatic cells may not behave identically to their 'young' ES cell counterparts.

Despite the perception that stem cells can miraculously cure disease, there are currently only 3 733 registered trials using forms of ES, AS and iPS cells (not all involving patients), according to ClinicalTrials.gov, a database of federally and privately funded clinical trials that are being conducted across 178 countries.³

Only 3 of these registered trials are using ES cells and all are, as yet, without data to substantiate therapeutic success. The trials are privately funded by biotechnology companies in the USA, and do not involve injection of ES cells but rather the use of ES cell lines that have been induced to differentiate into particular cell types. The world's first ES cell clinical trial was given Food and Drug Administration clearance in 2009. It involves the injection of ES cells, directed to an oligodendrocyte precursor cell lineage, into 10 patients with acute spinal cord injury within 10 days of injury.^{4,5} The trial has not been without controversy; it was initially halted, but has since resumed.⁶ The remaining 2 trials have just begun to determine the effects of sub-retinal injection of ES cell-derived retinal pigment epithelial cells in patients with various forms of macular degeneration.

There has been more therapeutic success with AS cells. Indeed, doctors have been performing bone marrow transplants for decades to treat leukaemia, multiple myeloma and lymphoma, with the success of these transplants now known to be due to the presence of haematopoietic stem cells in the bone marrow, which are capable of differentiating into any blood cell type. The bone marrow also contains mesenchymal stem (MS) cells, which can differentiate into bone, cartilage, fat, cardiomyocytes and neural cells. MS cells can also be isolated from adipose, umbilical or muscle tissue, and then perpetuated *ex vivo* before autologous cells are selected and re-introduced into the patient. Such MS cell transplantation has showed varied degrees of success in humans, raising debates about the safety thereof.⁷⁻⁹ Nevertheless, there are almost 200 clinical trials using MS cells registered on *ClinicalTrials.gov*, with the vast majority in China or Korea.³

In summary, there is no doubt that stem cells, in all forms, have enormous potential to benefit the patient. The medical reality is

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that their efficacy and safety in patients has not been established unequivocally.

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