Stem Cells: The Future of Personalised Medicine?

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**ABSTRACT:** After hitting the headlines in the 1960s, stem cell therapy has been the subject of great optimism in the treatment of many conditions. Discoveries of new procurement methods for various stem cells has allowed the technology and research to progress to a stage where real therapeutic alternatives are potentially viable.

In order to determine the direction to move forward, it is first important to analyse the data that has been collected across well researched stem cell types (Embryonic Stem cells, Induced pluripotent stem cells, Haematopoetic stem cells and Mesenchymal stem cells) as well as emerging stem cell types (Very-small-embryonic-like stem cells, Spermatogonial stem cells and Parthenogenetic stem cells).

Whilst by no means conclusive, the data does support the optimism surrounding these cells. Whilst stem cells may be embraced as the future of personalised medicine, following these pilot trials, research needs to become more focussed to allow advancement.

**KEYWORDS:** stem cell, embryonic stem cell, induced pluripotent stem cell, hematopoietic stem cell, mesenchymal stem cell, very-small-embryonic-like stem cell, spermatogonial stem cell, parthenogenetic stem cell


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**Introduction**

Stem cells first hit the news headlines in the 1960s. After an initial burst of excitement, there has been an ebb and flow to the interest that has developed in them. The first step in the advancement of personalised medicine came through the usage of embryonic stem cells (ESCs), progress that was met with some ethical scrutiny due to the requirement of human embryos. The ability to procure stem cells from a variety of sources meant that research continued with a great degree of anticipation surrounding the use of stem cell therapy, a true therapeutic alternative in the pursuit of personalised medicine.

Throughout the ages, humans have constantly searched for ways to prolong both the lifetime and quality of life. Stem cells are the latest in a long line of treatment options, being heralded as the basis for personalised medicine and biological insurance. Though currently in an early phase of development with evidence still being sourced, stem cells may have a place in almost all branches of medicine.

When examining the various types of stem cells that have been discovered across the previous half a century, it is initially important to define stem cells as an entity. Stem cells are undifferentiated cells that are the building blocks of specialised tissue through their ability to differentiate into multiple cell lineages. It is however, their ability to self-renew indefinitely that makes them so potentially useful in potential therapy.¹

While there are numerous types of stem cells that have been discovered, defined, and researched, it would be beyond the practical scope of this review to analyse each of them. Consequently, the stem cells examined in this review are the ones that the author believes are well understood and those that may present with the greatest potential in the future.

The full use of a stem cell may be primarily defined by its differentiative potential. ESCs and induced pluripotent stem (iPS) cells are the most investigated pluripotent stem cell lines, proven to be able to form any cell type from all three blastodermic layers, as is the definition.² Their use has been primarily limited due to a number of issues and consequently
multipotent stem cell, which can differentiate specific to one germ line\(^1\) have undergone more research and procured a stronger evidence base. While naturally occurring progenitor cell populations exist in many organ systems, the main multipotent stem cell types undergoing research are haematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs).

**Embryonic Stem Cells**

The successful isolation of ESCs from human blastocytes in 1998\(^4\) is defined as a prominent step in the early stages of stem cell therapy. While evidence of such pluripotent cells had already been discovered in vitro,\(^5\) the derivation of the first human line was yet uncharted territory. The discovery and potential characteristics of these cells drew great interest from the scientific community with Pera et al.

\(^6\) stating “the scope for even the more obvious applications envisioned for human cells with these properties is breathtaking.”

There are two major avenues that have been explored to procure these cells. The first approach utilised spares embryos that have not been required during IVF therapy,\(^7\) cells that would under normal circumstances be discarded anyway. On the other hand, ESCs could be created using nuclear transplantation, a process that introduces a somatic cell nucleus into an enucleated oocyte.\(^8\),\(^9\)

The problems that circulated ESCs when they were first presented still exist today. The most prominent and commonly referred to drawback is the ethical dilemma that these cells present. The varied stances worldwide governments take on this delicate topic are evident through the diversity of the restrictions placed on their use around the world.\(^10\) The primary ethical consideration that is highlighted concerns the potential viability of these cells. Logically, the usage of parthenogenetic and non-viable embryos should bypass any ethical issues and it can be argued that the moral differentiation between spare embryos and those created specifically could be negligible.\(^7\) Therefore governing laws should be equivalently applied as opposed to selective allowances. The only drawback of such a system is the potential for exploitation and could result in a slippery slope to harvesting embryos.

A second pitfall that may prevent these cells from ever reaching clinical use is concerning literature, which may highlight potential tumorgenesis in some cells derived from ESC lines.\(^11\) This literature is by no means conclusive and these claims still require confirmation or rejection. Due to the nature of procurement, autologous ESCs can never be used therapeutically, which creates a potential for immune responses.

Regardless of potential concerns, research manages to progress and there are increasing numbers of ESC lines available\(^12\)–\(^19\) in addition to the numerous animal lines that have also been derived.

Such strong ethical issues will have notable impacts on the progression of a treatment to human clinical trials. The notable change appeared in 2009 when, arguably surprisingly, approval was granted to run the first human ESC trial.\(^20\) The trial was set up with patients presenting with complete thoracic spinal cord injuries.\(^21\) There were high hopes for the results of this clinical trial, primarily based on a similar animal study that was carried out.\(^22\) Mid study results reported that the application of the cells was relatively safe and feasible with only minor side effects, such as nausea and low magnesium.\(^21\) The study was abandoned prior to completion, the reasons believed to be business orientated to allow focus on cancer therapy.\(^23\) The backlash from this decision was considerable but the company has urged that the four patients who underwent therapy have been monitored to not only obtain more data but also to ensure that their quality of life was not impacted due to the cancellation of the trial. Currently no new reports have emerged regarding clinical use of these ESCs and what started off as a very exciting prospect may ultimately end in a blind alley, leaving no choice but to focus efforts on treatment through other stem cell types.

**Induced Pluripotent Stem Cells**

IPS cells are artificially created through the reprogramming of human somatic cells. Reprogramming would be a single-time intervention with the cell possessing full pluripotency without the need for constant reprogramming.\(^24\) While several genetic manipulations have been suggested to achieve this result, the first and arguably simplest requires the manipulation of only four genes within the cell, a model demonstrated in both mouse and human cells.\(^25\),\(^26\) The differentiation capabilities and biological potency of iPS cells mirror ESCs\(^27\) without presenting the same scale of ethical disagreement.

The mode of reprogramming has proven crucial to the potential that these cells possess. Utilisation of viral vectors was the initial methodology adopted almost universally. However, concerning data on tumour and teratoma formation post-transplant\(^28\) was attributed to the use of viral vectors and prompted immediate investigation into alternative reprogramming techniques. Continuing research has proved successful with several breakthroughs of successful somatic cell reprogramming via alternative means reported.\(^29\)–\(^31\) This shows the marked progression of iPS cells and they may still have a key role to play in clinical therapy in the future with a trial highlighting the ability of iPS cells to improve or slow retinal degeneration.\(^32\)

There is currently no published clinical data on the use of these iPS cells and while there have been rumours about a trial undergoing approval and recruitment\(^33\) until an official announcement occurs, these rumours must be treated as such.

**Haematopoetic Stem Cells**

Classically derived from bone marrow, HSCs have routinely been used in the treatment of blood disorders for three decades. Natural differentiation, specific to multiple lines within the haematopoietic system, has proved invaluable to allow their use in such a way.\(^34\) As research has progressed, procurement from alternative sources, such as umbilical and cytokine-mobilised blood, has been discovered.\(^35\) A subset of HSCs known as CD34+ mononuclear cells are thought to be the key factor in
regenerative potential and have been attempted to be exploited specifically in clinical trials. It is thought that they induce the proliferation of progenitor cells, however, no role has yet been confirmed for these cells.\textsuperscript{36,37} Evidence has demonstrated that these cells can be mobilized using granulocyte-colony stimulating factor (G-CSF),\textsuperscript{38} a technique hypothesised as a potential treatment option for a number for disease states.

To analyse all the data regarding HSCs is not only difficult, it is beyond the scope of this review. The non-clinical data of HSCs is vast with a variety of conditions investigated through a plethora of end-points. It is important to note that even with such a bank of evidence, the data regarding the use of HSCs does not yet meet or exceed FDA regulations and consequently cannot be licensed for clinical practice.

A problem that is commonly found is the apparent contradictions found in literature. This not only serves to highlight the infant nature of this therapy but also the lack of complete understanding on it. In the treatment of infracted myocardial cells, data has been released claiming that bone marrow transplant leads to new proliferating myocytes, believed to be a consequence of the HSCs,\textsuperscript{39} while conflicting data disputes the ability of HSCs to transform into cardiomyocytes.\textsuperscript{40} The same disagreement occurs within studies relating to HSC differentiation within the liver. Two main theories exist; one claiming that the effect is achieved through cell transdifferentiation as a consequence of microenvironmental cues,\textsuperscript{41,42} while the other refutes it claiming that cell fusion, most likely with Kupffer cells, accounts for the improvement noted in liver function.\textsuperscript{43,44} These are only two examples in what is a catalogue of evidence that appears to exist in a contradictory vicious circle.

Irrespective of such varied non-clinical data, approvals have been granted and this treatment option has been taken forward to human trials. The most advanced trials appear to be in the treatment of myocardial infarction, mirroring the immediate interest in this condition in the early progression of animal trials. Randomised trials investigating HSC interventions through both mobilisation and infusion have taken place and moved forward.\textsuperscript{45–47} There appears to be directly conflicting data among various trials, a trait that was evident in the non-clinical data. While the trials appear to deem the therapy safe, albeit one raises concern of an increased rate on restenosis, the data on the efficacy is conflicted. One trial deems the HSC therapy to improve left ventricular function while another determines that it has no effect on it, although all the trials determine that the therapy appears to have a positive effect on the myocardium in some fashion.

The data in the treatment of liver cirrhosis is more synchronous, albeit more in its early years. While the Myocardial Infarction (MI) trials are investigating efficacy as well as safety, the focus of the liver cirrhosis trials is firmly set on safety. Stem cell infusion, mobilisation, and a combination have been attempted\textsuperscript{48–51} with all trials bar one\textsuperscript{49} deeming it safe. This may be attributed to the re-infusion through the hepatic artery specifically as opposed to the HSCs themselves. However, these speculations cannot be confirmed nor denied until further data has been sourced.

A spike in interest regarding autologuous transplantation in the treatment of autoimmune disease emerged with several Phase I/II trials reporting results across a variety of diseases.\textsuperscript{52–55} All the evidence highlights the high mortality rates that are associated with diseases of such a nature. Coupled with the nature of the trials, the determination of procedure-related morbidity and mortality are comparative to the disease-related. On the whole, the preliminary data appears promising, although associated with significant risks. This prompts further investigation, perhaps with more stringent inclusion and exclusion criteria to allow fuller understanding in very specific disease states.

It is evident that HSCs may have a role to play across almost all branches of medicine. As appears to be a common drawback, the large scope for treatment options indicates that no single disease has yet procured enough evidence necessary for full FDA approval. This remains the single most prominent requirement for HSC research and continues to progress. At such a rate, provided that the evidence returns positive results, HSCs may soon vie for a place among the standard therapies.

**Mesenchymal Stem Cells**

Described as “plate-adhering, fibroblast-like cells possessing self-renewal ability with the capacity to differentiate into multiple mesenchymal cell lineages,”\textsuperscript{56} MSCs are another form of stem cells extractable from the bone marrow. Less invasive procurement has been suggested through harvesting MSC populations in menstrual blood and the endometrium, but these are yet to be common practice. Though naturally multipotent, MSCs can be manipulated to form cells from all three blastodermic layers.\textsuperscript{57}

An initial Phase I trial demonstrated that the MSCs can be collected, expanded, and re-infused into patients safely.\textsuperscript{58} These MSCs were only used as supporting cells for HSC transplantation, primarily due to the rarity of MSC cell populations in comparison to HSCs. Trials soon progressed and MSC osteological therapy took its first steps when rat models demonstrated clinically significant bone regeneration.\textsuperscript{59} Progression expanded in MSC within the musculoskeletal system with tendon repairs carried out in rabbits,\textsuperscript{60} the data reporting a significant biochemical improvement, however, not accompanied by visual changes in its structure.

As appears common with adult human stem cells, migration occurs to sites of injury, commonly demonstrated and tracked in patients presenting with myocardial infarctions.\textsuperscript{61} This suggests a role for MSCs in tissue regeneration and is supported by data that determined improved angiogenesis following an autologous bone marrow transplant,\textsuperscript{62} data that could be attributed to MSC plasticity in the formation of endothelial progenitor cells, which have shown to play a role in neurovascularization.\textsuperscript{63,64}
Common with HSCs, some MSC trials are just starting out while others have managed to gain momentum and expansion into further advanced clinical studies. While bone marrow was thought to be the primary source for stem cells, in 2005 MSCs were successfully extracted and infused from liposapirate. While the secondary objective was to stimulate the healing of Crohn’s fistula, the nature of the trial did not allow reliable results, though progression to Phase II trials was suggested. Trials such as these exist in isolation and currently require further evidence for expansion. Recovery following chemotherapy in breast cancer patients is such a study, the first trial to utilise MSCs therapeutically. Indicating positive results, such a trial is included in the long list of stem cell therapies that did not progress beyond initial excitement.

Most stem cell therapies have focussed on autologous application. The use of allogeneic MSCs have been investigated in two human trials, one in adult patients and the other in paediatric subjects. Deemed safe and supported by an animal model investigating MI in pigs, this approach seems to have potential. Contrasting data suggests that the allogeneic nature of transplanted MSCs could induce an immune T cell response in the host, ultimately leading to a rejection of the transplanted cells. Such responses were not detected in the trials but the potential for severe adverse reactions exists, prompting the argument dictating that autologous stem cells would be the preferred choice. Counteracting evidence regarding rejection can be presented for allogeneic MSCs. Such cells have been used to counteract rejection in patients who have undergone allogeneic transplantation of other cells. While two very different disease states were investigated across a diverse patient demographic, both studies required ex-vivo expansion of donor MSCs prior to transplantation. The positive results from these studies cast a shadow over the debate of allogeneic compared to autologous transplantation. While both present with various advantages; as long as the risk of rejection cannot be categorically disproved in allogeneic MSC transplantation, it will not be able to compete with the risk-free nature of autologous cell transplantation.

Consistent with the problem associated with HSC evidence, the data for autologous MSC treatment is thinly spread out across a variety of focus areas. An initial trial investigating the effects of MSCs on stroke patients was expanded to a longer-follow up trial following the results. The shorter trial determined that the therapy was safe and feasible; but with only five patients in the treatment group, the results indicating improvement cannot be deemed reliable. These results were mirrored in the longer follow-up trial, however, it concluded that the recovery effect might be dependant on the specific characteristics of the patient. Nevertheless, further trialling is required on what may be a groundbreaking progress allowing the return of neural function following a stroke.

The high mortality and morbidity rates associated with MI open a desirable route of investigation to counteract it. Stem cells appear to improve left-ventricular function post-MI and this trend applies to MSC application as well. An expansion of this trial combined both MSCs and endothelial progenitors to restore myocardial function. The reasoning expands on the data highlighting the role of endothelial progenitors in neurovascularisation, which consequently when coupled with MSC application, should theoretically increase myocardial function to a greater degree post-MI.

Cirrhotic liver disease has also attracted attention with a culmination of four human clinical trials reaching similar conclusions. MSCs derived from different methods may hinder the validity of the comparisons among these trials, but the safety, feasibility, and apparent improvement in liver function is evident. Although two randomised trials were carried out, the nature of the investigation was primarily safety, with efficacy being investigated in parallel. The results from these tests indicate that phase III trials are recommended as this treatment option has potential, and according to one set of trials, the safety of MSCs surpasses that of HSCs, naming them the stem cell of choice in the treatment of cirrhotic liver disease.

The same set of problems appears to be evident across adult multipotent stem cells. Vast quantities of non-clinical data supported by scarce, primarily safety directed clinical trials spread across several disease fronts. However, the evidence is promising, potentially more so than HSCs, and MSCs may also have a future in personalised regenerative medicine. The same suggestions are aired with the call for more evidence, with a greater degree of follow up trials to allow such technology to assert a foothold in the medical industry.

Discussed above are the most prominent stem cell types. As research has progressed, a variety of stem cell types have emerged with controversy surrounding their usage. These are discussed briefly with potential view for clinical application.

**Very-Small Embryonic-Like Stem cells**

Indicated by the name, the cells possessed qualities typical of an ESC such as a large nuclei, narrow cytoplasm, and the presence of euchromatin. First identified in bone marrow in 2006, VSEL stem cells possessed pluripotent differentiation properties. As with other stem cell types, procurement locations have expanded and these cells have been found in cord as well as mobilised peripheral blood. Hypotheses have been made, suggesting that it is cells such as these and other non-HSCs present in bone marrow that are responsible for the plasticity that has been attributed to HSCs.

Pluripotency has also been shown by ESCs and iPS cells, but evidence indicates that VSEL stem cells do not contribute to teratoma formation, placing them in good stead to potentially be the choice stem cell as research progresses. Hypotheses have suggested that these cells are deposited during organogenesis and eventually give rise to less plastic stem cells, and therefore could play a fundamental role in the rejuvenation and regeneration of damaged organs.

Animal trials have proved successful spanning a variety of organ systems including cardiovascular, neurological,
gastrointestinal,90 and musculoskeletal systems.91 The results of the trials were varied and incomparable in quantity to other stem cell types. However, the results were sufficient to allow progression into human trials.

Human trials investigated patient presenting with myocardial infarctions92 and strokes.93 Both trials demonstrated VSEL stem cell mobilisation to the site of injury. While indicative of prognostic value, this technology is still in its infancy.

**Spermatagonal Stem Cells**

Namely, multipotent spermatogonal stem cells (SSCs) differentiate in the process of spermatogenesis. The most obvious clinical future for these stem cells is the restoration of fertility in pre-pubescent cancer patients who have undergone chemotherapy, with studies showing potential for preservation.94 Other factors that need addressing include the efficacy and safety of the methods, with particular attention to any malignant contamination that may re-appear post-transplant.95 While methods continue to advance towards a potential clinical application,96 the complete solution to the variable issues has not yet been determined. As with other multipotent stem cell lines, provided the technology becomes viable, there may be potential for these cells to be used in other areas of medicine such as transgenerational therapy or cell based organ regeneration.97

Note that it is also important to mention ovarian stem cells in this context. However there is a distinct lack of evidence surrounding their potential usage clinically.

**Parthenogenetic Stem Cells (PSCs)**

Parthenogenesis is simply defined as a form of asexual reproduction. The key difference lies in the growth and development of the embryos without any need for fertilisation. These pluripotent stem cells demonstrate the same characteristics as human ESCs in both replicative and differentiative capabilities.98 The research has progressed to allow the derivation of multiple human embryonic stem cell lines from parthenogenetic blastocysts.99,100 The establishment of these lines is a step forward in the clinical application of these stem cells. A breakthrough trial101 has demonstrated the “seamless” integration of PSCs derived cardiomyocytes into host myocardium. This was able to enhance myocardial function post-myocardial infarction and has presented itself as a very appealing option with PSC pluripotency, especially its cardiogenicity, being demonstrated.

NB. Cord derivative stem cells are one classification of stem cells that have not been discussed individually in this review article. It is however important to note the variety of stem cells that can be procured from human umbilical cord blood, some of which have been discussed above.

**Stem Cell Tourism**

The evidence above clearly presents that stem cell therapy as a whole still remains in the clinical experimentation stage and no therapy has a strong enough evidence base to be licensed by the FDA for standard clinical use. This raises an ethical dilemma concerning the numerous clinics that have appeared, which offer “stem cell therapies” to prospective patients. These clinics are in complete contrast to organisations offering storage facilities; the emphasis for which is that stem cell therapy may eventually have the potential and approval to be used out with clinical trialling. The data has proven that stem cell therapies, especially autologous minimally invasive ones, are not dangerous and carry very few side effects. Therefore their use may not cause any issues in terms of patient safety but there is no clear evidence that the treatment will provide any discernable benefit. While potentially a very profitable business, it may be one which raises eyebrows within the medical community at this current stage.

**Conclusion**

While the data is by no means conclusive, it does serve to highlight that the optimism surrounding stem cell therapy may be justified. The vast array of stem cell types at the disposal of researchers may act as a hindrance as opposed to an advantage as this treatment looks to step forward. This coupled with the vast spectrum that stem cell therapy can be used in has resulted in sporadic data, which cannot be compared reliably to give valid conclusions. Stem cells may be the future of personalised medicine, but the research needs to become more focussed to allow advancement. If the positive results are mirrored to the pilot trials and the technology proceeds with no hurdles, then there is potential for the adult stem cells to become FDA regulated for standard clinical use within the current generation.

**Author Contributions**

Conceived and designed the experiment: AI. Analyzed the data: AI and IA. Wrote the first draft of the manuscript: AI. Contributed to the writing of the manuscript: AI. Agreed to submit this paper.

**DISCLOSURES AND ETHICS**

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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