# *Editorial*

*A cautionary note*:

# Stem cell tourism

"*If I had Multiple Sclerosis or Parkinsonism, I would be getting stem cell therapy and I'd probably go offshore."* This may be the most popular opinion of desperate patients and their relatives.

Travelling abroad for medical treatment is a craze in current times. Many patients are travelling overseas on lucrative medical tourism packages. Stem cell tourism is becoming a common trend in recent years. However, our knowledge about safe stem cell therapy seems to be inadequate. Attractive media coverage on this recent trend seems to be never ending and thus raising concerns about patient safety issues. On behalf of Faculty of Medicine at Lincoln University College, Malaysia, we organized a Post Graduate seminar to spread general awareness among medical and allied health science faculty members and post graduate students regarding current status of stem cell therapy.

**Mesenchymal adult stem cells and its safety issues**

Adult stem cell therapy offered a 'very exciting prospect' of treatments in neurological and degenerative conditions and even heart disease. Clinical trials involving more than 100 patients showed clear benefits for the use of adult stem cells from bone marrow in myocardial infarction. Mesenchymal stem cells (MSCs) do have therapeutic potential. Research over the past ten years has revealed that these cells home in on damaged or inflamed tissues and have various roles in repair, releasing molecules that suppress an overactive immune system, stabilize newly forming blood vessels or prevent cells from dying.[1] Initial fears that these cells might take hold *in vivo* and become cancerous, subsided with evidence that they disappear after a short time in the body. In recent years there is a growing consensus that MSCs are safer than what researchers perceived earlier Based on the current clinical trials, MSC therapy appears safe. However, further larger scale controlled clinical trials with rigorous reporting of adverse events are required to further define the safety profile of MSCs.[2]

**Induced Pluripotent Stem Cells and risks**

Induced pluripotent cells of human origin (hiPSC) showed great therapeutic potential in pre-clinical studies. However, we are concerned about the potential risk of using these reprogrammed autologous cell lines which may often exhibit disease features similar to those of the patients from whom these cells were obtained. Despite the capacity of hiPSC to differentiate in a fashion similar to embryonic stem cells (ESC) into fully differentiated tissues, these reprogrammed cell lines show far more tumorogenicity than that of ESC as all the genes that have been used to promote hiPSC reprogramming have been linked to cancer in one way or another.[3]

**Embryonic stem cell research and related ethical issues**

Embryonic stem cell therapy carried a small risk of creating tumors in patients as well as of raising huge ethical issues about the destruction of human embryos. The field of embryonic stem cell research has already been plagued by exaggeration and misrepresentation, as three major journals have had to retract significant claims about progress in this field. This problem is exacerbated by the politicized climate in which the research is conducted and defended. It may also lie deeper, in a utilitarian ethic that in principle could justify unethical actions for admittedly worthwhile long-term goals. Such an ethic risks undermining the credibility of science, which must show a commitment to the facts that is independent of social and political goals.[4]

**Issues about discrepancies in clinical trials**

Many clinical trials have been undertaken but results are far from conclusive. Some claim significant improvements whereas others report no improvement for patients.

Unscrupulous claims for magic cures using stem cell therapy are threatening a promising field of stem cell research. Early-phase clinical trials have reported that adult stem cells are effective in treating myocardial infarction and cardiac failure cases, and many companies are moving quickly to tap into this potentially lucrative market.[5] But a comprehensive study that looked at discrepancies in trials investigating treatments that use patients' own stem cells, finds that only trials containing flaws, such as design or reporting errors, showed positive outcomes.[6]

A *BMJ* study, included all accessible randomized studies, and looked for discrepancies in design, methodology and reporting of results which identified more than 600 discrepancies, including contradictory claims for how patients were randomized, conflicting data in figures and tables, and statistically impossible results.
(http://www3.imperial.ac.uk/newsandeventspggrp/imperialcollege/medicine/heartandlunginstitute/newssummary/news_28-5-2015-15-8-22)

**Paradigm shift from stem cell therapy to cell free therapy**

It was claimed by several authors that stem cells differentiate or trans-differentiate to replace damaged cells *in vitro* and *in vivo*. Many researchers and clinicians now believe that the cells act by releasing molecules that cause inflammation, with an attendant growth of oxygen-delivering small blood vessels, in the damaged tissue. It has been increasingly observed that the transplanted MSCs did not necessarily engraft and differentiate at the site of injury but might exert their therapeutic effects through secreted trophic signals.[7]

According to this paradigm, in situations of blood vessel damage, the released pericytes transform to MSCs, are activated by the injury and respond to that tissue site by secreting a spectrum of bioactive molecules, (i.e., drugs) that serve to, first, inhibit any immune cell coming to survey the tissue damage and, thus, prevent autoimmune activities from developing. In addition, these secreted bioactive molecules, through their trophic activities, establish a regenerative microenvironment to support the regeneration and refabrication of the injured tissue. In this context, the MSCs serve as site-regulated, multidrug dispensaries, or "drugstores," to promote and support the natural regeneration of focal injuries.[8]

These MSCs secrete a variety of autocrine/paracrine factors, called secretome, that support regenerative processes in the damaged tissue, induce angiogenesis, protect cells from apoptotic cell death and modulate immune system. The cell culture medium conditioned by MSCs or osteogenic, chondrogenic as well as adipogenic precursors derived from MSCs has become a subject of intensive proteomic profiling in the search for and identification of released factors and microvesicles that might be applicable in regenerative medicine. Secreted molecules are key mediators in cell-cell interactions and influence the cross talk with the surrounding tissues. There is strong evidence supporting that crucial cellular functions such as proliferation, differentiation, communication and migration are strictly regulated from the cell secretome.

In recent years the analytical data on stem cell secretome is accumulating continuously, and thereby increasing interest given the potential use of these cells in regenerative medicine.[9]

**Stem cell tourism**

There has been a great deal of media coverage on stem cell tourism for cell therapy abroad which is offered as a commercial package. A panel of British doctors and scientists has warned of the risk to health and finances of visiting private stem cell clinics around the world.[10]

In conclusion, we would like to emphasize that there is long way to go before researchers will conclude about safe use of cell therapy or cell free therapy. "Medical tourism" for unproved uses of

stem cell therapy poses potential risks to patients. They may spend tens of thousands of pounds in the hope of an effective treatment for chronic degenerative conditions such as Parkinson's disease, multiple sclerosis, and some forms of retinal disease.

The stem cell researchers warned that the stem cell technology is used prematurely in therapeutic areas where there is little or no evidence of well defined clinical benefits and where the chances of success are many years or even decades away.

We are seriously concerned because the therapeutic use of stem cells is already being commercialized while the results of premature clinical trials are creating unrealistic hopes for patients.

This craze for stem cell tourism is diverting our attention and financial resources from intense pre-clinical studies that we need before designing more appropriate and safe stem cell therapy.[10]

In this article we played the role of a whistle blower to caution the helpless desperate patients and their relatives from visiting private stem cell clinics in less regulated countries being allured with exaggerated claims of stem cell therapy seeking magic cure.

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