Editorial

'Present Status and Future Trends in Adult and Embryonic Stem Cell Research'

Stem cells in general and pluripotent stem cells in particular have gained tremendous interest in the recent years, primarily driven by the hope of finding cures for several debilitating human diseases through cell transplantation (regenerating medicine). Pluripotent stem cells have the inherent ability to reproduce indefinitely and have the capability to produce all the 220 different types of cells constituting the human body and thus offer tremendous therapeutic potentials. The isolation of human embryonic stem cells (hESCs) from embryos and their successful culture in the petrii dish in 1998 [1] has been considered the biggest breakthrough of the 21st century. This has been followed by another remarkable breakthrough in 2006 when scientists demonstrated for the first time that such pluripotent stem cells could be produced from adult somatic tissues by reprogramming without having to use human embryos [2]. These pluripotent stem cells are called the induced pluripotent stem (iPS) cells. Production of iPS cells has been considered as the biggest discovery of this decade. Both hESCs and iPS cells are pluripotent and are highly versatile and offer tremendous therapeutic potential for finding cures for many incurable diseases such as diabetes, Parkinson's, Alzheimer's, and many other diseases via stem cell therapeutic in the next decade or so. Adult stem cells, particularly the haematopoietic stem cells (HSC) and the neural stem cells (NSC) have been in literature for some decades and during the last few years such adult stem cells have also been derived now from almost all the adult tissues, skin, pancreas, liver, heart, kidney, including those from body fluid like amniotic fluid and even menstrual blood, umbilical chord blood. Adult stem cells have already been successfully used in human therapies for many years. The in depth information gained from adult stem cell research during all these years has played a very critical and significant role in advancing the current field of pluripotent stem cell research that is now poised towards regenerative medicine.

Stem cells are a promising source of biological material for regenerative medicine and recently the concept of producing autologous or customized pluripotent stem cells from somatic cells (iPS technology) has attracted the attention of investigators and clinicians who seek a feasible methodology for cell therapy that can be applied to the treatment of patients with degenerative diseases and organ failure as well as experimental applications for drug discovery, screening and toxicology, etc.

These stem cells whether adult, embryonic or induced have unique characteristic feature that is defined in terms of their differentiation potential for example totipotent (ability to form all 220 types of cells including placenta), pluripotent (ability to produce all 220 type of cells), multipotent (ability to produce many but not all cells) and unipotent (restricted to produce only one type of cell). The fate of such stem cells is determined in embryo during the developmental process. Mammalian development is considered a unidirectional process during which there is a progressive loss of developmental potential. It begins with the formation of a unicellular zygote and ends with the establishment of the 220 specialized cell types of the mammalian body. Stem cell populations is thought to have a characteristic epigenetic pattern that correlates with its differentiation potential that could be explained by C. H. Waddington's `epigenetic landscape' model (Fig. **1**). It relates to a marble rolling down a hill into one of several valleys illustrates the declining developmental potential of individual stem cell populations. At each bifurcation point, the potential of the marble (cell) to choose different routes (cell fates) diminishes. The totipotent and pluripotent stem cells sit at the top and the adult stem cells that are generally multipotent sit in the middle of such landscape. Recent molecular studies have demonstrated that such stem cells populations are maintained largely by their epigenetic state. Similarly differentiation of stem cells to specific lineages is also determined by epigenetic landscape or mechanisms.

This supplementary issue is an attempt towards understanding some aspects of adult and pluripotent stem cell research and the progress towards their potential therapeutic use. Understandably the way this field is moving and growing, majority of papers have been on hESCs, some on adult stem cells and a few scholarly written reviews in the relevant field of

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reprogramming. To date there have been a number of transitional but minimal translation approaches more with adult than embryonic stem cell-derived cells. However, recently there is a record number of preclinical animal trials with cells derived from pluripotent stem cells including from iPSC for spinal chord injury, ischaemic heart and brain, Parkinson's, diabetes type1 and other diseases as a proof of principle that there is a gain of function. However, whether this gain of function is the result of trophic effect or actual integration of transplanted cells into the host system remains an open question. There are no clinical trial but for a recently approved by FDA from Geron Corporation (Menlo Park, California, USA) for hESC-derived oligodendroglial precursor cells for spinal chord injury patients and now also for patients with macula degeneration. Major concern in using pluripotent stem cell-based trials lies in their safety as any undifferentiated cells remained has the propensity of causing tumours and secondly these cells still remain allogeneic and likely to be rejected by the host and thus requires the use of anti-rejection drugs. Major emphasis is thus to develop robust system for large scale propagation of homogeneous populations of pluripotent cells using bioreactor. Understanding the molecular mechanism of pluripotency in these cells is important as also highlighted by a paper by Methichit in this issue that has identified a GLP-1 receptor on hESCs and iPS cells to up regulating pluripotency by engaging a number of micro RNAs regulating apoptosis in these cells. Equally important is the development of robust protocols to obtain purified lineage specified cells from these pluripotent cells and the fail-safe mechanism to eliminate any undifferentiated cells in such population that may cause tumours. Gao and co-workers in this issue described the use of 3D scaffold system coaxing efficient derivation of beta cells from hESCs.

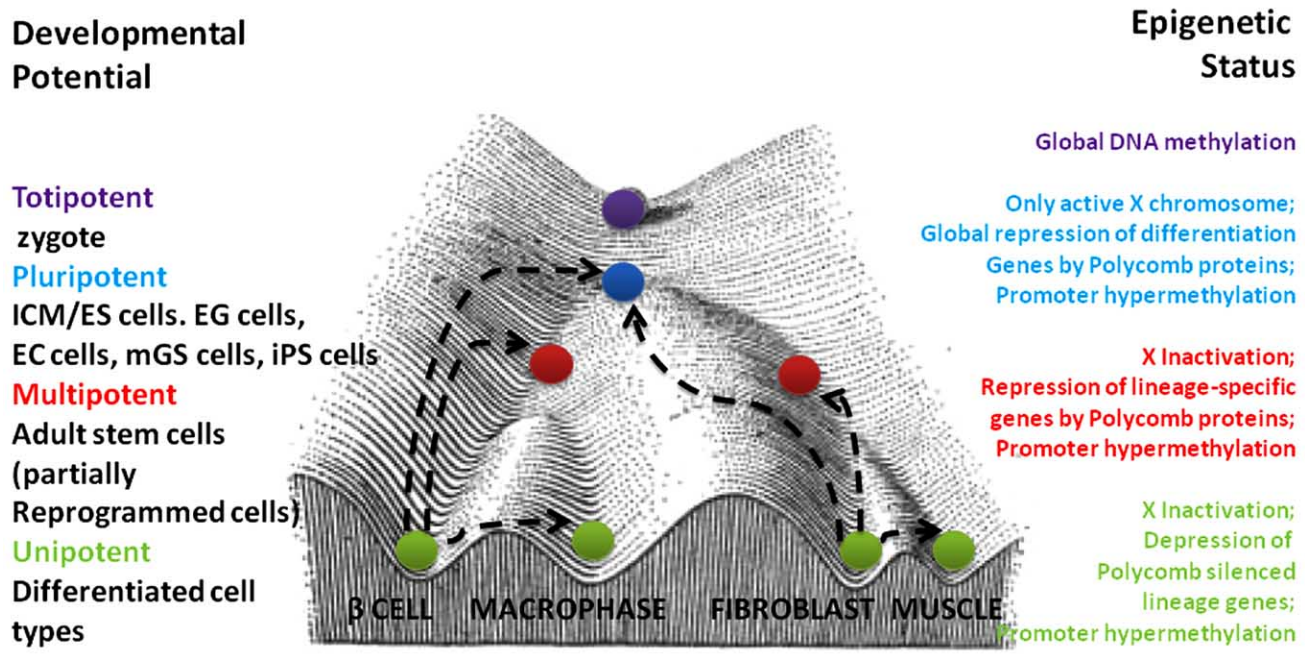

Fig. (1). The developmental potential and epigenetic states of cells at different stages of development. A modification of C. H. Waddington's epigenetic landscape model, showing cell populations with different developmental potentials (left) and their respective epigenetic states (right). Developmental restrictions can be illustrated as marbles rolling down a landscape into one of several valleys (cell fates). Colored marbles correspond to different differentiation states (purple, totipotent; blue, pluripotent; red, multipotent; green, unipotent). Examples of reprogramming processes are shown by dashed arrows [3].

Using the search terms "stem cells" and "brain" identified more than 300 clinical trials evaluating the use of adult stem cells to treat hypoxic/ischemic encephalopathy, cerebral palsy, multiple sclerosis, amyotrophic lateral sclerosis, neuronal ceroid lipo-fuscinosis, Parkinson's disease and spinal chord injury and others. These trials primarily involved the use of MSC/HSC-derived cells. Recently number of other adult stem cells derived from sources like umbilical cord, amniotic fluid and including menstrual blood (see Allickson *et al.* in this issue) have been used.

Before a large scale, multicenter clinical trials for efficacy with proven stem cells are possible, number of issues related to their safety, optimal cell dosage, delivery methods and *in vivo* cell tracking mechanisms need to be optimised. Cell therapy is a

new way of human therapeutics; it requires different regulatory frame work and delivery mechanisms and a different mind set for engaging biotech and biopharmaceuticals. Human stem cell biology is driving the promise of novel regenerative therapies into clinical trials. Although the pharmaceutical industry has embraced stem cells as tools in drug discovery, few companies have taken the risk to deliver stem cell-based medicines.

Kuldip S. Sidhu
(*Guest Editor*)

Stem Cell Lab,
Faculty of Medicine,
School of Psychiatry,
University of New South Wales,
Sydney, Australia
Fax: +6129385 3938
Tel: +6129385 3938
E-mail: k.sidhu@unsw.edu.au

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