

Roadblocks to Stem Cell Translation: A Commentary



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Received Date: September 23, 2015 Accepted Date: October 29, 2015 Published Date: November 6, 2015

Citation: Sidhu, K. Roadblocks to Stem Cell Translation: A Commentary. (2015) J Stem Cell Regen Bio 1(1): 6- 8.

Introduction

During the last few decades there has been a revolution in small molecules (the first pillar of human medicine) and biologics (the second pillar of human medicine) as frontiers in human medicine making a significant change in human health outcome. In the current decade the stem cells including other types of therapeutic cells are evolving for another revolution, the third pillar of human medicine. However, the intricate biology and complexities of living cells and their integration with host tissue pose a whole new challenge not encountered before in human medicine. But nevertheless stem cells can offer cure rather treatment for various ailments particularly those involving loss or degeneration of specific cells like beta cells in Diabetes, and specific neurons in spinal cord injury, Alzheimer's and Parkinson's diseases respectively^[1].

Stem cells towards therapeutics is relatively a new area but has assumed nearly a mythical status in attracting tremendous enthusiasm amongst scientific community and general public alike. There seems an increase inputs in terms of human resources, funding and infrastructure development in this field all over the world but its actual translation to the ground needs further thinking. The interest in this field is high partly because the way it has been put across to all of us with intense media coverage and promise of therapeutic values and other uses. No doubts the potential applications could be tremendous but there are number of issues/hurdles that have to be addressed before stem cell translation becomes reality.

Roadblocks and Challenges

Logistical

There is still a huge gap between overall public expectations and the scientific reality to accomplish clinical translation. However, there are unprecedented developments seen recently in this field with proof of principle emerging for number of diseases that currently have no cure but only management, like Alzheimer's, Parkinson's spinal cord injury, where stem cell-based therapies (regenerative medicine) can offer respite. While attention is focused primarily on their potentials in regenerative medicine, stem cells are gaining a stronghold in drug development, toxicological appraisal, and biomarker discovery - a move that may bring in a paradigm change in human medicine and therapeutics. Despite these progresses, there remain scientific, technical, logistic, financial and administrative/regulatory challenges and obligations that are required to be met to move this field forward towards translation. Although, overtly these may be seen as playing impediments in the way of stem cells translation.

A successful business model for stem cells translation to clinics impinges upon what type of stem cells are being considered - adult or embryonic including patient-derived induced pluripotent stem cells (iPSC) for such studies and also whether the ensuing therapies are autologous or allogeneic. The latter is favoured by the big pharma and industry and easy to regulate. The adult stem cell (hematopoietic and bone marrow) transplantation has a long history, and are morally and ethically more acceptable, although not necessarily gone through the rigour of traditional drug discovery pathway. But these cells have become a part of the main stream treatments for many malignancies and some genetic diseases. Similarly stem cell-derived skin graft transplantation is



following the same route. The Pluripotent stem cells, however, are still battling despite some significant advances and building hopes for diseases like macular degeneration, spinal cord injury, skin grafts and perhaps for some neurodegenerative diseases. There are some moral ethical and safety issues associated with these cells. It may be mentioned here that unlike small molecules and biologics that work on the principle of turning on/off of biological systems, stem cell-based therapies may be more predictable provided integrated properly in circuits such that the milieu/niche of the tissue brings about homeostasis and thus regulate their functions facilitating normalcy. This remains the most active area of research in this field^[1].

The landscape of stem cell translation is new and complex and requires liberal investments. An average cost of a pharmaceutical drug to deliver to the market is around 1.4 billion US \$ and it is likely to be more for stem cells-based therapy and that cannot be supported with public funding. Thus a typical drug delivery model won't work, and an alternative logistic and financial model such as Alpha Clinics proposed by California Institute of Regenerative Medicine to achieve widespread clinical application requires due diligence. Given the newness of this area, there remain uncertainties and risks involved that are hampering private investments in this field. Big pharma and corporate investors are shying away because of these risks. However, similar scepticism for investments was there for DNA recombinant technology and human genome projects; both are now providing dividend far excess than investments made. It is envisaged that despite this scepticism, profitable cell therapeutics will evolve following the route of new start up companies to attract major investors and or by logistic mergers of existing small companies. Developing cell therapies is far riskier and costly than developing research tools. Consequently, pharmaceutical companies and other investors including venture capitalists remain hesitant to invest into it. The start up venture is always risky, and it is also true for stem cell companies. It is clouded with cumbersome requirements and over expectations, and very tough and low venture capitalists. A successful business model should ensure return on investments, an easy exit strategy and is possible only with an interdisciplinary approach, a new paradigm in which pharma, early stage biotech and academia work together.

With minimal interest from venture capitalists and big pharma, it is considered that a different system is needed to evolve partnership of stem cell scientists with industry. The role of biotechnology sector in regenerative medicine is likely to be broader, providing materials, services, and cell manufacturing, suggesting much greater commercial opportunities in the clinical application of cell therapies. In addition, special government initiatives like the 2004 proposition 71 (public bond to fund scientific research) in California that led to the establishment of the California Institute of Regenerative Medicine for 3 billion US\$ and now Japan's 21.4 billion ¥ stimulus package for stem cells and iPSC work (Nature 28th Feb 2013) are steps in the right direction. Government special tax rebates/reforms in this business is another way of encouraging biotech companies and entrepreneurs investing in this area. This is particularly more relevant in the absence of involvement of big pharma in this field. Some stimulus packages in R&D in stem cells through government agencies like NHMRC, ARC, and CSIRO in Australia and likewise in other countries by creating special research groups

focussing exclusive in this area will be helpful. Non-to-profit organisations, philanthropists, and foundation funds all can make a difference^[1].

The regenerative medicine (therapeutics) is a new concept and despite a good science behind it, there is no single harmonised guiding principle that can be used to describe the preclinical development path or model for this therapeutics. Several specific technical issues like safety, efficacy, viability and tracing the transplanted cells are the inherent challenges in stem cell-based therapeutics. The existing regulatory framework for clinical trials with stem cell products is not clear or explicit and this gray area is a significant roadblock for transition to clinics. Perhaps the route followed by the blood and bone marrow transplantation initiatives may offer respite i.e. the need-based control human trials and case studies. However, sprouting of spurious stem cells clinics worldwide and the associated patient tourism is a big concern that needs addressing perhaps by proper educational initiatives in this area.

Scientific

The actual integration of stem cells with the host tissue is a real problem encountered in most studies. That is true even with proven therapy like HSCs, the number of integrating cells is rather low and the therapy is effective only because of the trophic effect of the transplanted cells systemically. Only 2-10% of stem cells have been demonstrated to be incorporated for longer time and almost none after 3 months^[2]. The cells death is encountered in the host ischemic or inflammatory environments, and the transplanted cells become susceptible to low oxygen and the hostile inflammatory cytokines and including the reactive oxygen species. Attempts are being made to acclimatise or modify these cells *ex vivo* so that they survive better in the host using antiapoptotic and other supporting factors as in cardiac heart diseases^[2]. But the functional integration remains poor and generally integrated cells are eventually eliminated by the host immune system. The quality control of transplanted cells is another area of great importance for integration. Removing residual pluripotent cells is absolute critical to prevent tumour formation. There is an intensive research on the level of differentiation that can be attained to achieve optimal integration.

Chronic diseases such as neurodegenerative are also associated with tissue fibrosis and changes in immunogenic profile, thus generating inhospitable milieu for the transplanted cells. Therefore the transplanted cells fail to survive better, compromising their functionality^[3,4]. Similarly, the hostile environment created by microglial activation and neuro inflammation arising concomitantly with the progression of neurodegenerative diseases may contribute to neuronal damage and influence grafted stem cells. Also the endothelial function is compromised by aging, cardiovascular, neurodegenerative and other chronic inflammatory diseases, suggests that an impaired microcirculation might not adequately support the transplanted cells. There is enough data to support that the vascular niche provides a paracrine environment for regeneration, thus such dysfunction induces defect in oxygen delivery, negatively impacting the anticipated paracrine affects through cascade of signals in the endothelium compromising the regeneration process^[2]. It is generally considered that intracellular milieu changes drastically during aging. This challenge needs an integrated therapeutic approaches such that will provide the proper niche for long term

survival of transplanted cells. For example, increasing vasculature could promote endogenous regeneration, and support the survival and function of transplanted stem cells.

New Frontiers

There are number of new frontiers in this stem cell therapeutics arena that need further fostering to make this field on a sound footing. These include harnessing the full potential of endogenous stem cells to repair and restore tissue structure and function by targeting and manipulating their niche externally by using small molecules and other growth factors. Similarly and particularly the latest approach of therapeutic reprogramming of diseased or normal healthy cells either *ex vivo* or *in vivo* to reverse and rescue the affected tissue or organ^[5]. An *ex vivo* approach to correct some of the genetic disorders in cells of a particular tissue by gene targeting is an emerging area making a significant progress. Also an another approach to cell regeneration would be to administer chemical or genetically engineered products directly to patients to specifically change the cell fates, or functions by mechanisms that can modify proliferation, differentiation, reprogramming, cell homing, within the defective tissue. This strategy would offer less invasive and more convenient 'individualized' precision treatments for individuals with various diseases and needs. Although these new frontiers may appear promising but have inherent difficulties to *in vivo* therapeutic reprogramming due to mismatch or lack of specificity for a given molecule. It also demands reinvigorating the pharmacokinetic properties of the therapy and safety issues.

Conclusion

At the moment transition of stem cells towards clinic is a cliff hanger and will continue to pose a series of scientific, clinical, technical and operational challenges over the coming decade. In order to be successful we need to develop an efficient, high-quality 'strategic hub' linking scientific institutions, clinical centres, big pharma and biotech companies so that transition is steady, cost-effective, efficient and with an insured return on investments. A novel and harmonized preclinical model system will be essential to promote and enhance this field, and to ensure more predictable anticipated recovery pathways will help infuse interests in stem cell technologies and their transition to clinic. The involvement of government's initiative in this field is critical and more so collective efforts through G20 nations is another way to bridge this gap in providing sufficient funding that this field needs at this stage to address both the logistic and scientific challenges.

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