Irfan-maqsood et al., 2015. Journal of Genes & Cells, 1(2): p, 40-45
doi: 10.15562/gnc.13

OPINION

Commercialization of Stem Cell Therapeutic Research: Bridging a Big Gap

Muhammad Irfan-Maqsood[1,2], Monireh Bahrami, Mahdi Mirahmadi,[1,3] Hojjat Naderi-Meshkin[1*]

1. Department of Stem Cells and Regenerative Medicine, ACECR-Mashhad Branch, Mashhad, Iran
2. Department of Biology, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran
3. Department of Biotechnology, ParsTechRokh Pharmaceuticals, Mashhad, Iran

ABSTRACT

Stem cell therapeutic research is passing through a transition phase between laboratory research and health industry. According to the US data registry of clinical trials, more than 4776 studies have been registered, 2882 have been completed whereas 1894 studies are in process. Surprisingly, in spite of having huge research, there are two commercialized stem cell therapeutic products in global market and these two products are also not approved by FDA. As it has been discussed in literature, stem cells have been considered as promising candidates to treat non-curable diseases like cancer etc. More than 80% successful clinical trials have been done showing no or little side effects with much better efficiency than pharmacokinetics but still stem cell research is far from being commercialized. The major reason of stem cells non-commercialization is the gap among clinicians, researchers, industry experts and policy makers. A multibillion dollar grants and a very strong communication system between doctors, researchers, industrial experts, policy makers, regulating authorities, are the pre-requisite to commercialize stem cell therapy.

Keywords: Current good manufacturing practice (cGMP), commercialization of stem cells, cellular therapy, clinical trials, non-curable diseases

Stem cell therapy has been recommended as a novel way of treatment for various diseases like cardiovascular, diabetic, neurological diseases, spinal and orthopaedic injuries, etc. A number of optimization techniques have been approved for clinical studies using stem cells [1, 2]. In recent years, stem cell therapy has been considered as a promising candidates in regenerative medicine to replace or regenerate damage tissues via differentiation [3] or paracrine effects [4]. 4776 studies are registered on US registry for clinical trials (www.clinicaltrials.gov) till 2014. The geographical distribution of these clinical trials are given in Figure 1.

* **Correspondence**:
hojjat_naderi@jdm.ac.ir

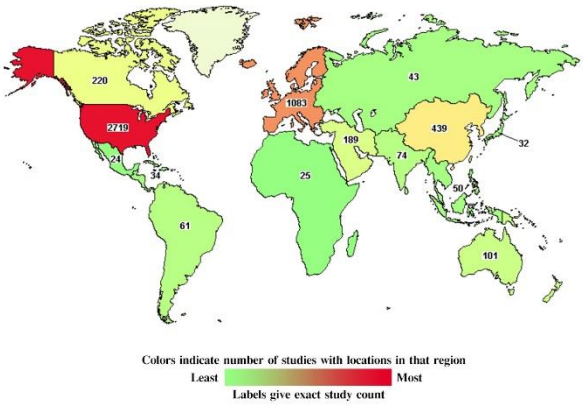

Figure 1: Geographical distribution of stem cells clinical studies (source, www.clinicaltrials.gov).

Hematopoietic and bone marrow stem cells are top cells used in stem cell therapy accounting 36% and 34% of total studies, respectively followed by neural stem cells (14%, mesenchymal stem cells (11%), adipose derived stem cells (4%) and embryonic stem cells (1%) as shown in Figure 2.

A tremendous growth has been observed in last decade in stem cell research especially MSCs, with a ratio of 100% increase as shown in Figure 3.

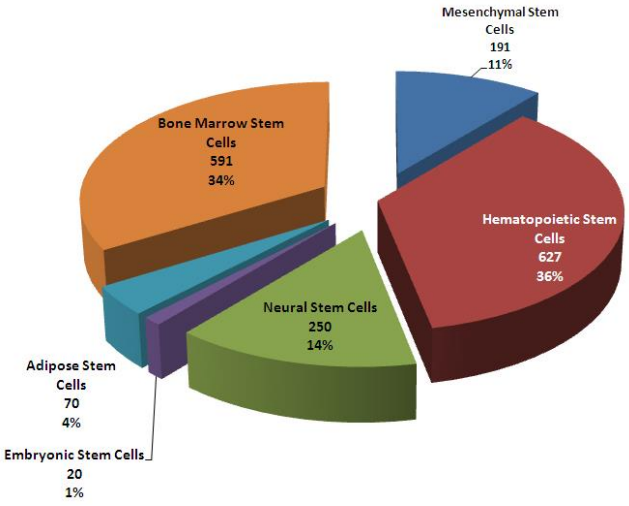

Figure 2: Involvement of stem cells in global clinical research (source, www.clinicaltrials.gov).

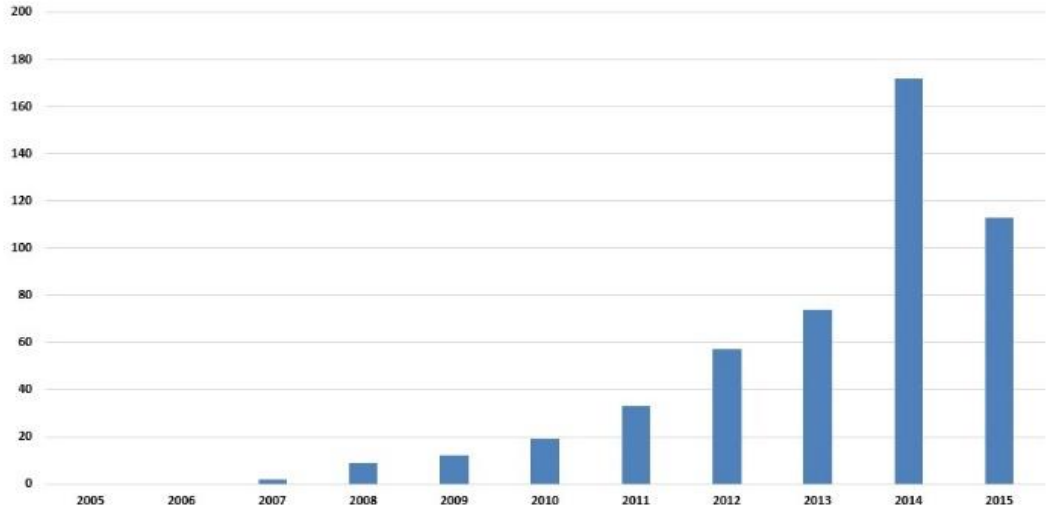

Figure 3: Number of Clinical Trials Using mesenchymal stem cells (source, www.clinicaltrials.gov)

Being dramatic increase in stem cell research, challenges faced by researchers have been reduced and improved efficiency has been observed with every passed year [5]. A number of challenges are still faced by the researchers like clinical grade stem cells production, teratomic behaviour, escape of grafted cells, possible microbial contaminations etc. [6, 7] as shown in Figure 4. It can also be said that unfortunately stem cell researchers are unaware of cGMP protocol.

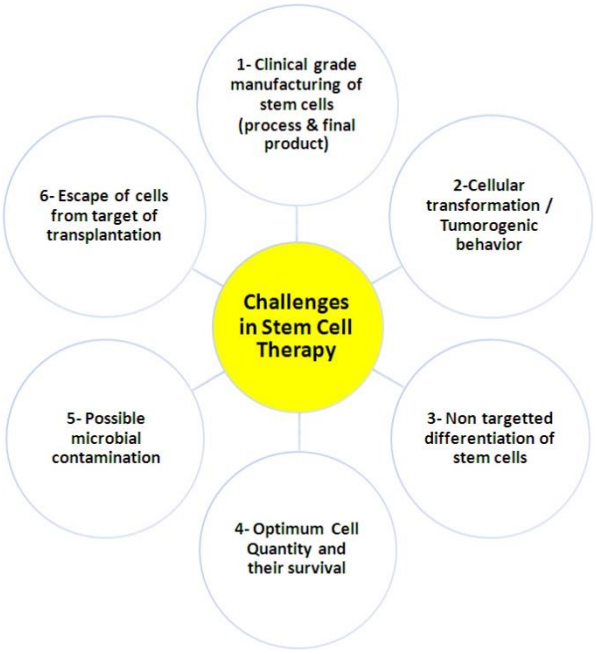

Figure 4: Challenges being faced in Stem Cell therapeutic research.

Clinical Grade Production of Stem Cells and cGMP Protocol:

First step for clinical grade production is testing their regenerative potential as pre-clinical studies on animal models such as rats, porcine, monkey, etc. The efficiency of characterized stem cells can be investigated both *in vivo* and *in vitro*. After having successful and promising pre-clinical data, the R&D team ensures clinical grade production of stem cells and follow cGMP protocol for phase I and II monitoring. After successful results from phase I and phase II, phase III clinical trials can be started and protocol can be finalized for commercial production after having greater than 99% efficiency as compared with other existing current methods. If data is compromised in phase I and II, results may be referred again to R&D team for further optimization and standardization to ensure protocols for clinical grade productions. Flow chart of cGMP protocol for commercialization of stem cells is given in figure 5 [8, 9].

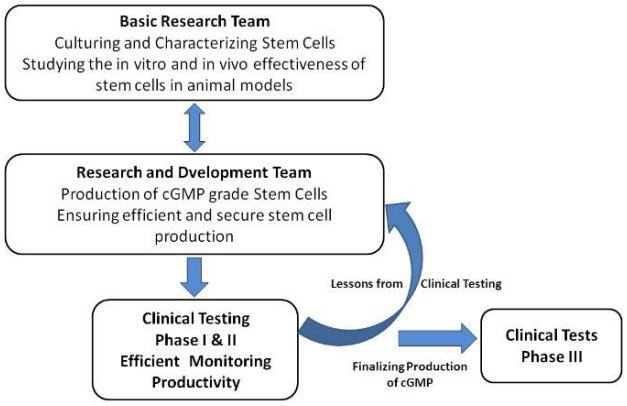

Figure 5: Work flow on the clinical grade (cGMP) production of stem cells.

Establishment of Stem Cell Commercialization Organizations:

To commercialize/transform stem cell research or to transform stem cell research into health industry, a number of proposals are given by different stem cell scientists who explained the strategies to implement research into clinics [10]. Commercialization organization should bridge the gap between researchers and doctors to commercialize therapeutic researchers. Cell therapy is a type of advanced therapeutic medicinal products (ATMPs) which must comply with current good manufacturing practice (cGMP) before applications which require a huge capital investment and expertise in skills. Pharmaceutical companies are the best examples of organizations who can commercialize stem cell research as they are well

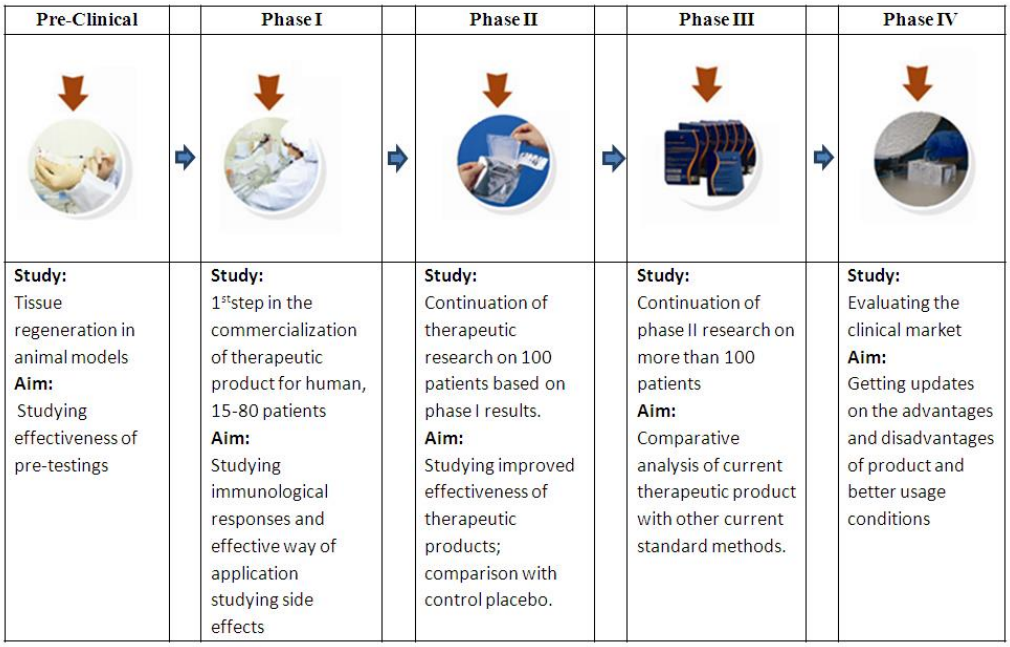

Figure 6: Pre-clinical and clinical testing phases to commercialized stem cell research.

aware about cGMP protocol [11]. When we consider the history of stem cell research, we find that unfortunately big pharmaceutical companies have shown a little or no interest in stem cell commercialization [12] that is may be due the short shelf life of cellular products. A very strong coordination and dedication is required as a number of small biotech incorporations have shown their potential to commercialize cell therapeutic research [13]. A number of countries such as US, Brazil and Korea have endorsed public funds to perform stem cell clinical trials on human by establishing inter-disciplinary applied research centers [14] as model projects to reduce the gap between basic & clinical research and their introduction in public health system.

Commercialization of cell therapeutic research should maintain a strong pipeline, along with a planned growth of intellectual property (IP). Following three steps should be followed by an organization working for the commercialization of therapeutic sciences; (1) Measuring effectiveness in pre-clinical trials in appropriate animal models. (2) Validating safety for effective pre-clinical therapeutic products (3) Obtaining FDA regulatory approval for human clinical trials with safe and effective pre-clinical products [15].

To gain money for advanced production of cell therapeutic products, one strategy is obtaining allowance of easy-to-produce and low cost products (as first-line treatment option), partner or obtain financing for manufacture, sales, and distribution of this first product; and concurrently advance the second-line treatment option (products need pass through clinical trials) with further investment rounds and revenues. The first easy-to-produce medical goods can financially guarantee advance forward the production of high-cost second-line product.

Business Perspectives:

Transformation of research into clinical practice requires forging of strong coordination among organizations such as universities, hospitals, patient associations etc. Most important organizations are biotech and pharmaceutical industries. Along with huge investment, these firms need huge moral and ethical supports for clinical commercialization. Ethical authorities should support companies after a complicated review process of their innovations and patents in clinical researches starting from the basic research to registration. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that product candidates

or proprietary technologies may infringe. A capital investment is sought to provide cash resources for bringing product candidates up to and through Phase I clinical trials. A second round of investment will then be required to perform and complete Phase II clinical trials for the candidate new cell therapeutic product. These Phase II trials are expected to be complete in one year, at which point, an R&D alliance or a Series C financing event will fund Phase III clinical trials and other R&D operations, as needed [16].

Research and development activities, and pre-clinical studies and clinical trials, are subject to extensive regulation by FDA and other regulatory authorities in the United States and other countries. Regulatory difficulties that may be out of our control could adversely affect ability to develop pipeline products [17]. When a cell therapeutic research is launched, it requires approximately 3-4 years, earning patients and doctor's confidence to enter into the profit stage. 4th year, usually can be considered the time for enhanced productions of cellular products and the time for a huge investment. Companies may face investment difficulties in 4th year because of the low growth in first 3-4 years. To maintain company profit flow, following options can be considered. (1) Grants by public and private institutes, (2) by outsourcing, and/or (3) by collaborations with university partners and other joint venture partners to enhance competitive edge providing expertise, technical facilities and special needs, and ultimately, manufacturing, testing and commercialization support.

Conclusion:

The gap among researchers, policy makers, ethical regulation authorities and industry experts is the main reason of failure to gain patient-doctor confidence and to commercialize stem cell research. Stem cell research is gaining a huge attention by researchers worldwide but it is failed to get popularity among medical practitioners to start clinical trials and to start cell therapy in their routine clinical practice. Absence of local regulatory authorities to monitor and approve stem cell research is also a major challenging task in stem cell commercialization. In a number of states and regions of the world, stem cell regulating authorities are composed of medical practitioners and policy makers who have little or no information on regarding stem cell biology. A very strong communication system and multidisciplinary efforts are required to get stem cell research from laboratory to health sector.

Acknowledgement:

ACECR-Mashhad branch highly thank Khorasan-e-Razavi governorship for their generous grant to setup clean rooms for the production of clinical grades stem cells for clinical practice.

Conflict of Interest:

We declare no conflict of interest with any organization or person.

References:

1. Ghasroldasht, MM, Irfan-Maqsood, M, Matin, MM, Bidkhori, HR, Naderi-Meshkin, H, Moradi, A, and Bahrami, AR, *Mesenchymal stem cell based therapy for osteo-diseases.* Cell Biol Int, 2014. **38**(10): p. 1081-5.
2. Naderi-Meshkin, H, Bahrami, AR, Bidkhori, HR, Mirahmadi, M, and Ahmadiankia, N, *Strategies to improve homing of mesenchymal stem cells for greater efficacy in stem cell therapy.* Cell Biol Int, 2015. **39**(1): p. 23-34.
3. Lavoie, JR and Rosu-Myles, M, *Uncovering the secretes of mesenchymal stem cells.* Biochimie, 2013.
4. Maumus, M, Jorgensen, C, and Noel, D, *Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: Role of secretome and exosomes.* Biochimie, 2013.
5. Naderi, H, Matin, MM, and Bahrami, AR, *Review paper: critical issues in tissue engineering: biomaterials, cell sources, angiogenesis, and drug delivery systems.* J Biomater Appl, 2011. **26**(4): p. 383-417.

6. Law, S and Chaudhuri, S, *Mesenchymal stem cell and regenerative medicine: regeneration versus immunomodulatory challenges.* Am J Stem Cells, 2013. **2**(1): p. 22-38.
7. Naderi-Meshkin, H, Matin, MM, Heirani-Tabasi, A, Mirahmadi, M, Irfan-Maqsood, M, Edalatmanesh, MA, Shahriyari, M, Ahmadiankia, N, Moussavi, NS, Bidkhori, HR, and Bahrami, AR, *Injectable hydrogel delivery plus preconditioning of mesenchymal stem cells: exploitation of SDF-1/CXCR4 axis towards enhancing the efficacy of stem cells' homing.* Cell Biol Int, 2015.
8. Sensebe, L, *Clinical grade production of mesenchymal stem cells.* Biomed Mater Eng, 2008. **18**(1 Suppl): p. S3-10.
9. Sensebe, L, Bourin, P, and Tarte, K, *Good manufacturing practices production of mesenchymal stem/stromal cells.* Hum Gene Ther, 2011. **22**(1): p. 19-26.
10. Cuende, N and Izeta, A, *Clinical translation of stem cell therapies: a bridgeable gap.* Cell Stem Cell, 2010. **6**(6): p. 508-12.
11. Trounson, A, Baum, E, Gibbons, D, and Tekamp-Olson, P, *Developing a case study model for successful translation of stem cell therapies.* Cell Stem Cell, 2010. **6**(6): p. 513-6.
12. McKernan, R, McNeish, J, and Smith, D, *Pharma's developing interest in stem cells.* Cell Stem Cell, 2010. **6**(6): p. 517-20.
13. Lysaght, MJ, Jaklenec, A, and Deweerd, E, *Great expectations: private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics.* Tissue Eng Part A, 2008. **14**(2): p. 305-15.
14. Daniels, JT, Secker, GA, Shortt, AJ, Tuft, SJ, and Seetharaman, S, *Stem cell therapy delivery: treading the regulatory tightrope.* Regen Med, 2006. **1**(5): p. 715-9.
15. Hourd, P, Chandra, A, Medcalf, N, and Williams, DJ, *Regulatory challenges for the manufacture and scale-out of autologous cell therapies*, in *StemBook*. 2008: Cambridge (MA).
16. Kola, I and Landis, J, *Can the pharmaceutical industry reduce attrition rates?* Nat Rev Drug Discov, 2004. **3**(8): p. 711-5.
17. Feigal, EG, Tsokas, K, Viswanathan, S, Zhang, J, Priest, C, Pearce, J, and Mount, N, *Proceedings: international regulatory considerations on development pathways for cell therapies.* Stem Cells Transl Med, 2014. **3**(8): p. 879-87.