Journal of Clinical & Experimental Cardiology

Parsons, J Clin Exp Cardiolog 2013, S11
DOI: 10.4172/2155-9880.S11-e001

Editorial Open Access

# Cellular Medicine for the Heart-the Pharmacologic Utility and Capacity of Human Cardiac Stem Cells

**Xuejun H Parsons**[1,2]*

[1]San Diego Regenerative Medicine Institute, San Diego, CA 92109, USA
[2]Xcelthera, San Diego, CA 92109, USA

Human stem cells are extremely attractive for therapeutic development because they have direct pharmacologic utility in clinical applications, unlike any cells originated from animals and other lower organisms that are only useful as research materials. The human stem cell is emerging as a new type of pharmacologic agent of cellular entity that is much more complex in structure, function, and activity than the conventional drug of molecular entity, which is usually comprised of simple chemicals or compounds. Since the etiologies of most diseases that involve both molecular and cellular processes are much more complex than simple chemicals or molecules, conventional chemical drugs are often severely limited by the molecular entity of the compound that usually targets or blocks certain pathological molecular pathways, which would otherwise be harmful to common molecular pathways shared in normal cellular processes of vital tissues and organs, thus, cause severe toxic side effects that may outweigh the benefits. For instance, a drug for weight loss may cause severe damage to the heart. In addition, the therapeutic effects of conventional drugs of molecular entity provide only temporary or short-term symptomatic relief but cannot change the prognosis of disease. As a result, millions of molecular leads generated in mainstream of biomedical research from animal studies and studies of other lower organisms have vanished before even reach clinical trials, or for a few lucky ones, in clinical trials. In the last few decades, despite of many animal leads, no drug of molecular entity has ever been approved by FDA as a new treatment for heart disease and failure for humans.

In contrast, the human stem cell has the potential for human tissue and function restoration that the conventional drug of molecular entity lacks. The ability of a human stem cell, by definition, to both self-renew and differentiation makes it a practically inexhaustible source of replacement cells for many devastating or fatal diseases that have been considered as incurable, such as neurodegenerative diseases and heart diseases. The pharmacologic activity of human stem cells is measured by their extraordinary cellular ability to regenerate the tissue or organ that has been damaged or lost, such as the heart in the case of human cardiac stem cells. Therefore, the pharmacologic utility of human stem cells cannot be satisfied only by their chaperone activity, if any, to produce trophic or protective molecules to rescue existing endogenous host cells that can simply be accomplished by a drug of molecular entity. Although a vast sum of government and private funding has been spent on looking for adult alternates, so far, only human cardiac stem/precursor/progenitor cells originated from pluripotent human embryonic stem cells (hESCs), derived from the inner cell mass (ICM) or epiblast of human blastocyst, have shown such cellular pharmacologic utility and capacity adequate for heart regeneration [1-6].

The heart is the first organ formed from the cells of the ICM or epiblast of the blastocyst in early embryogenesis. The mature contracting cardiac muscle cells, which are known as cardiomyocytes and which contribute to most of the structural volume of the heart, are terminally differentiated and unable to regenerate in the adult heart. There is no evidence that stem/precursor/progenitor cells derived from other sources, such as bone marrow, cord blood, umbilical cord, mesenchymal stem cells, patients' heart tissue, placenta, or fat tissue, are able to give rise to the contractile heart muscle cells following transplantation into the heart [1,2]. Therefore, there is mounting skepticism about the existence of endogenous human cardiac stem cells after birth. Despite numerous reports about cell populations expressing stem/progenitor cell markers identified in the adult hearts, the minuscule quantities and growing evidences indicating that they are not genuine heart cells and that they give rise predominantly to smooth muscle cells rather than functional contractile cardiomyocytes have diminished any enthusiasm [7]. In recent years, reprogrammed or trans-differentiated adult cells, as a result of being backed by excess sum of government and private funding, have been rekindled as the adult alternates. However, somatic cell nuclear transfer and factor- or chemical-based reprogramming are incapable of restoring a correct epigenetic pattern of pluripotent hESCs [8,9]. The embryo-originated hESCs are not only pluripotent, but also incredibly stable and positive, as evident by that only the positive active chromatin remodeling factors, but not the negative repressive chromatin remodeling factors, can be found in the pluripotent open epigenome of hESCs [10-13]. Although pluripotent, the reprogrammed adult cells, either originated from induced pluripotent stem cells (iPS cells) by over expression of known oncogenes or derived from cloned embryos by somatic cell nuclear transfer, are made from adult cells, therefore, their epigenomes carry many negative repressive chromatin remodeling factors and unerasable genetic imprints of adult cells that pluripotent hESCs do not have [8,9,14]. As a more direct alternate to iPS cells known cardiac-fate determining genes or chemicals were recently used to transdifferentiate or reprogram fibroblasts or tissues into induced adult cardiac progenitors and cardiomyocytes by genetic engineering or induction with extremely low efficiencies [15]. Such major drawbacks as abnormal gene expression accelerated aging, immune rejection, not graftable, and extremely low efficiencies, have severely impaired the utility of reprogrammed or trans-differentiated somatic cells as viable therapeutic approaches. Although small molecules used to induce hESC lineage-specific therapy derivatives are usually safe developmental signal molecules and morphogens [1,3], it should be cautious of the small molecules used in the reverse process to induce iPS cells or trans-differentiation, which are known toxic cancerogenic chemicals with too dangerous or even lethal side effects to be used for patients.

Given the limited capacity of the heart for self-repair, there is a large unmet healthcare need to develop hESC-based therapies to

***Corresponding author:** Xuejun H Parsons, PhD, President, San Diego Regenerative Medicine Institute, San Diego, CA 92109, USA, Tel: 858-274-1621; Fax 858-581-3213; E-mail: parsons@SDRMI.org

**Received** June 05, 2013; **Accepted** June 07, 2013; **Published** June 10, 2013

**Citation:** Parsons XH (2013) Cellular Medicine for the Heart-the Pharmacologic Utility and Capacity of Human Cardiac Stem Cells. J Clin Exp Cardiolog S11: e001. doi:10.4172/2155-9880.S11-e001

provide optimal regeneration and reconstruction treatment options for heart disease and failure. However, realizing the developmental and therapeutic potential of hESC derivatives has been hindered by the inefficiency and instability of generating clinically relevant functional cells from pluripotent cells through conventional uncontrollable and incomplete multi-lineage differentiation [1]. Recent advances and technology breakthroughs in hESC research have overcome some major obstacles in bringing hESC therapy derivatives towards clinical applications, including establishing human stem cell technology platforms for defined culture systems for *de novo* derivation and maintenance of clinical-grade pluripotent hESCs and lineage-specific differentiation of pluripotent hESCs by small signal molecule induction [1-5,10-13]. Formulation of minimal essential defined conditions for sustaining embryonic pluripotence renders hESCs directly and uniformly converted into a specific neural or cardiac lineage by small signal molecule induction [1-5,10-13]. Such milestone advances and medical innovations in hESC research enable generation of a large supply of high purity clinical-grade hESC neuronal and heart muscle cell therapy products as powerful cellular medicines that can offer pharmacologic utility and capacity for CNS and heart regeneration that no conventional drug of molecular entity can. Currently, these hESC cardiomyocyte therapy derivatives are the only available human cell sources with adequate capacity to regenerate the contractile heart muscles, vital for heart repair in the clinical setting [1-5]. The availability of human cardiac stem cells originated from embryo sources in high purity and large supply with adequate myocardium regenerative potential will greatly facilitate developing safe and effective cell-based therapies against heart disease and failure. Transforming pluripotent hESCs into fate-restricted therapy derivatives dramatically increases the clinical efficacy of graft-dependent repair and safety of hESC-derived cellular products, bringing regenerative medicine to a turning point.

## References

1. Parsons XH, Teng YD, Moore DA, Snyder EY (2011) Patents on Technologies of Human Tissue and Organ Regeneration from Pluripotent Human Embryonic Stem Cells. Rec Pat Regen Med 1: 142-163.
2. Parsons XH (2012) Mending the broken heart - Towards clinical application of hESC therapy derivatives. J Clinic Exp Cardiology 3: e116.
3. Parsons XH, Teng YD, Parsons JF, Snyder EY, Smotrich DB, et al. (2011) Efficient derivation of human cardiac precursors and cardiomyocytes from pluripotent human embryonic stem cells with small molecule induction. J Vis Exp : e3274.
4. Parsons JF, Smotrich DB, Gonzalez R, Snyder EY, Parsons XH, et al. (2012) Defining conditions for sustaining epiblast pluripotence enables direct induction of clinically-suitable human myocardial grafts from biologics-free human embryonic stem cells. J Clin Exp Cardiology S9: 001.
5. Parsons XH (2012) MicroRNA Profiling Reveals Distinct Mechanisms Governing Cardiac and Neural Lineage-Specification of Pluripotent Human Embryonic Stem Cells. J Stem Cell Res Ther 2.
6. Zhu WZ, Hauch KD, Xu C, Laflamme MA (2009) Human embryonic stem cells and cardiac repair. Transplant Rev (Orlando) 23: 53-68.
7. Passier R, van Laake LW, Mummery CL (2008) Stem-cell-based therapy and lessons from the heart. Nature 453: 322-329.
8. Kim K, Doi A, Wen B, Ng K, Zhao R, et al. (2010) Epigenetic memory in induced pluripotent stem cells. Nature 467: 285-290.
9. Gore A, Li Z, Fung HL, Young JE, Agarwal S, et al. (2011) Somatic coding mutations in human induced pluripotent stem cells. Nature 471: 63-67.
10. Parsons XH (2012) The Dynamics of Global Chromatin Remodeling are Pivotal for Tracking the Normal Pluripotency of Human Embryonic Stem Cells. Anat Physiol .
11. Parsons XH (2012) An Engraftable Human Embryonic Stem Cell Neuronal Lineage-Specific Derivative Retains Embryonic Chromatin Plasticity for Scale-Up CNS Regeneration. J Regen Med Tissue Eng 1.
12. Parsons XH (2013) Human stem cell derivatives retain more open epigenomic landscape when derived from pluripotent cells than from tissues. J Regen Med 1: 2.
13. Parsons XH, Parsons JF, Moore DA (2012) Genome-Scale Mapping of MicroRNA Signatures in Human Embryonic Stem Cell Neurogenesis. Mol Med Ther 1.
14. Tachibana M, Amato P, Sparman M, Gutierrez NM, Tippner-Hedges R, et al. (2013) Human embryonic stem cells derived by somatic cell nuclear transfer. Cell 153: 1228-1238.
15. Islas JF, Liu Y, Weng KC, Robertson MJ, Zhang S, et al. (2012) Transcription factors ETS2 and MESP1 transdifferentiate human dermal fibroblasts into cardiac progenitors. Proc Natl Acad Sci U S A 109: 13016-13021.

This article was originally published in a special issue, **Cardiac Stem Cells** handled by Editor(s). Dr. Rosalinda Madonna, University of Texas Medical School, USA