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Mending the Broken Heart--Towards Clinical Application of Human Embryonic Stem Cell Therapy Derivatives

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Cardiovascular disease (CVD) is a major health problem and the leading cause of death in the Western world. In the United States, around 5 million survive heart failure but live with insufficient cardiac function, and about 550,000 new cases are diagnosed annually. Heart attacks, known as myocardial infarction (MI), are the main cause of death in patients with CVD. Around 1/3 of the patients suffering from heart attacks each year die suddenly before reaching the hospital. In the remaining patients who survive their initial acute event, the damage sustained by the heart may eventually develop into heart failure, with an estimated median survival of 1.7 years in men and 3.2 years in women.

In the adult heart, the mature contracting cardiac muscle cells, known as cardiomyocytes, are terminally differentiated and unable to regenerate. To date, the lack of a suitable human cardiomyocyte source with adequate myocardium regenerative potential has been the major setback in regenerating the damaged human heart, either by endogenous cells or by cell-based transplantation or cardiac tissue engineering [1,2]. Damaged or diseased cardiomyocytes are removed largely by macrophages and replaced by scar tissue. Although cell populations expressing stem/progenitor cell markers have been identified in the adult hearts, the minuscule quantities and growing evidences indicating that they are not genuine heart cells have caused skepticism if they can potentially be harnessed for cardiac repair [1,2]. 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, or fat tissue, are able to give rise to the contractile heart muscle cells following transplantation into the heart [1,2]. Recently, reprogrammed or trans-differentiated adult cells, which can be traced back to 80th, have been rekindled as alternatives. However, adult cell-reprogrammed or trans-differentiated cells not only have the same problems of adult cells, such as accelerated aging, immune rejection, and not graftable, but also have additional problems of extremely low efficiencies (<0.5%) to reprogram or trans-differentiate as well as abnormality, therefore, they are not useful for cell therapy in clinics. So far, the need to regenerate or repair the damaged heart muscle, known as myocardium, has not been met in today's healthcare industry [1-3]. Heart transplantation with the donor organ has been the only definitive treatment for end-stage heart failure. For millions living with the damaged heart, there is no alternative definitive treatment available at present time. For patients who need heart transplantation, there is an acute shortage of donor organs. Many patients die while waiting on the shortlist.

Pluripotent human embryonic stem cells (hESCs), derived from the inner cell mass (ICM) or epiblast of human blastocyst, proffer unique revenue to generate a large supply of cardiac lineage-committed stem/precursor/progenitor cells as well as functional cardiomyocytes as adequate human myocardial grafts for cell-based therapy [3]. Due to the prevalence of CVD worldwide and acute shortage of donor organs or adequate human myocardial grafts, there is intense interest in developing hESC-based therapy for heart disease and failure. The hESCs and their derivatives are considerably less immunogenic than adult tissues [1-3]. It is also possible to bank large numbers of human leukocyte antigen isotyped hESC lines so as to improve the likelihood of a close match to a particular patient in order to improve the engraftment and survival efficiency, and minimize the potential risk and side-effect of immune rejection following transplantation [1-3]. However, in order to generate a large supply of uniform functional cells as the cell therapy product targeting for a particular disease, how to channel the wide differentiation potential of pluripotent hESCs efficiently and predictably to a desired lineage has been a major challenge for clinical translation of the therapeutic potential of hESC derivatives. In addition, most currently available hESC lines were derived and maintained on animal feeder cells and proteins; therefore, such hESCs have been contaminated with animal biologics and cannot be used for patients in clinics [3]. In hESC-differentiating multi-lineage aggregates, such as embryoid bodies (EBs), only a very small fraction of cells (<4 %) spontaneously differentiate into cardiomyocytes [1,2]. Immune-selection has been used to isolate and enrich populations of immature cardiomyocytes from hESC-differentiating EBs [1-3]. Such enriched hESC-derived immature cardiomyocytes could generate small grafts and function as the biological pacemaker in animal infarcted models [4]. Although such hESC-derived cardiomyocytes can partially remuscularize the injured heart and attenuate the progression of heart failure in animal models of acute myocardial infarction, the grafts generated by cell transplantation have been small and insufficient to restore heart function or to alter adverse remodeling of chronic infarcted models following transplantation [5-7]. Functional enhancement in preclinical animal models by such hESC-derived cardiomyocytes through conventional multi-lineage germ-layer induction strategies has been limited to mid-term at most, equivalent to perhaps a few months in humans, and there is no evidence that the underlying mechanism depends on the contractile properties of the transplanted human cells [1-7].

To tackle the shortcomings in conventional approaches, we have resolved the elements of a defined culture system necessary and sufficient for sustaining the epiblast pluripotence of hESCs, serving as a platform for *de novo* derivation of animal-free therapeutically-suitable hESCs and effectively directing such hESCs uniformly towards clinically-relevant lineages for clinical translation [3,8-13]. To achieve uniformly conversion of pluripotent hESCs to a specific lineage,

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we have employed the defined culture system capable of insuring hESC proliferation to screen a variety of small molecules to identify conditions necessary for directing hESCs exclusively towards a lineage-specific fate without an intervening multi-lineage differentiation stage. We found that pluripotent hESCs maintained under the defined culture conditions can be uniformly converted into a specific neural or cardiac lineage by small molecule induction [3,8-13]. Our breakthroughs have overcome some major obstacles in bringing hESC therapy to clinics, enabling *de novo* derivation of clinical-grade cGMP compatible stable hESC lines from human blastocysts that have never been contaminated by animal cells and proteins, and direct conversion of such pluripotent hESCs into a large supply of clinical-grade functional human cardiac precursors and cardiomyocytes to be translated to patients for mending the damaged heart. Our novel approach of hESC cardiac lineage-specific differentiation direct from the pluripotent stage using small molecule induction is a major milestone towards clinical application of hESC therapy derivatives, offering the benefits in efficiency, stability, safety, and scale-up production of clinical-grade hESC therapy products in cGMP facility over current multi-lineage differentiation strategies [11-13]. The heart is the first organ formed from the cells of the ICM/epiblast of the blastocyst in early embryogenesis. The hESC-derived embryonic heart cells resemble the heart cells in human development; therefore, they have the powerful potential to form human contractile heart muscle as well as the cardiovascular structure with intact 3D geometry and vasculature of the whole heart. The availability of a large supply of clinically-grade human myocardial grafts in high purity and large quantity with adequate potential to mend the damaged heart will accelerate the development of safe and effective cell-based therapy for heart disease and failure that affect millions of survivors and currently have no cure. It makes heart disease and failure possible to be the first major health problem to be resolved by clinical translation of the advances of hESC research.

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