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HUMAN STEM CELLS AND CARDIAC REVITALIZATION (NEW EXPERIENCE IN TAJIKISTAN)

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Stem cells have remarkable potential to grow in more than 200 types of cells that the adult human body holds. Regenerative medicine by using stem cells is at the vanguard of health care poised to offer solutions for many of today's incurable diseases. Bone marrow derived stem cells have been used *in vitro* to generate bone, cartilage, tendon, ligament, meniscus, intervertebral disc, fat, muscle, and nerve. The aim of this review is to describe the stem cell therapy in Tajikistan and its position in the word. In Tajikistan for the first time the laboratory for investigation of stem cell created in Avicenna Tajik State Medical University, Dushanbe at November 29, 2009 and the first clinical study for heart stem cell therapy started at March 9, 2010. In this study, autologous transplantation of bone marrow derived $CD133^+$ was undertaken with the high degree of success for a cohort of patients with coronary artery disease.

Keywords: *Regenerative medicine, human stem cells, cardiac revitalization, coronary artery disease, bone marrow derived $CD133^+$.*

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ЧЕЛОВЕЧЕСКИЕ СТВОЛОВЫЕ КЛЕТКИ И РЕВИТАЛИЗАЦИЯ СЕРДЦА (НОВЫЙ ОПЫТ В ТАДЖИКИСТАНЕ)

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Стволовые клетки обладают удивительной способностью давать начало более чем 200 видам клеток, имеющимся в организме взрослого человека. Регенеративная медицина, являясь авангардом передовых технологий и используя стволовые клетки, может решить многие проблемы, связанные с неизлечимыми заболеваниями. Сегодня стволовые клетки, полученные из костного мозга, используются *in vitro* для выращивания кости, хряща, сухожилия, связки, мениска, межпозвоночного диска, жира, мышцы и нерва. Целью данного обзора является предоставление информации о состоянии клеточной терапии в Таджикистане и её позиции в мире. В Таджикистане исследование стволовых клеток впервые было проведено в ТГМУ им. Абуали ибни Сино 29 ноября 2009 года, а первое клиническое применение стволовых клеток при ишемической болезни сердца началось 9 марта 2010 года. В данном исследовании, с высокой степенью успеха, группе пациентов с коронарной болезнью сердца была проведена аутотрансплантация $CD133^+$ клеток, извлечённых из костного мозга.

Ключевые слова: *регенеративная медицина, человеческие стволовые клетки, ревитализация сердца, ишемическая болезнь сердца, стволовые клетки $CD133^+$.*

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Stem cells have remarkable potential to grow in more than 200 types of cells that the adult human body holds. By serving as a kind of body repair system, they can theoretically divide without limit to restore other cells as long as the person or animal is still alive. When a stem cell divides, each new cell may remain either a stem cell or become another type of cell with more specialized function, such as a muscle cell, a red blood cell, or a brain cell [1].

Stem cell research provides knowledge on how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising field of science also directs scientists to investigate the possibility of cell-based therapies to treat diseases, often referred to as regenerative or restorative medicines [2]. Stem cells are today one of the most fascinating areas of biology. But as in many fields of scientific inquiry, stem cell research raises scientific questions as quickly as they generate new discoveries.

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division [3]. The second is that under certain physiologic or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the spinal cord cells or other [4-7]. Several ways to obtain or derive stem cells from early mouse embryos discovered more than 40 years ago. Many years of detailed study of the biology of mouse stem cells led to the discovery, in 1998, of how to isolate stem cells from human embryos and grow the cells in the laboratory. These are called human embryonic stem cells [8].

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, stem cells in developing tissues give rise to the multiple specialized cell types that make up the heart, lung, skin, and other tissues. In some

adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease.

One of the many reasons for the attention stems from the potential of these cells to regenerate tissues without the production of scar tissue that is generally associated with healing processes. With any new technology comes a myriad of terms, many of which are poorly defined with regard to stem cells. One of the most difficult distinctions when discussing stem cells is defining what is a "stem cell". Stem cells are defined as clonogenic, self-renewing progenitor cells that can generate one or more specialized cell types [9].

A Russian-American scientist – Alexander A. Maximow proposed (1908) the term "stem cells". He stated that all the blood cells have a single precursor cell [10]. The first distinction to be made is between embryonic and adult stem cells. Adult stem cells are those which arise or are obtained from any post-natal source. Embryonic cells arise from an embryo, often in an 8 cell or less stage. Embryonic cells that are capable of generating an entire organism are referred to as "totipotent". A more restricted subset of cells that is capable of forming tissues from each of the germ layers is referred to as "pluripotent" cells or, when generating an even more restricted subset of cells, called "multipotent" [11]. It has long been thought that each tissue type had a resident population of adult stem cells present to maintain the tissue. The recent idea of plasticity suggests that adult stem cells can de-differentiate then re-differentiate down another cell lineage or transdifferentiate to another lineage. An example would be a hematopoietic stem cell (mesodermal in origin) that becomes neuron (ectomdermal origin). In laboratory model, Induced pluripotent stem cells (iPSC) produced by reprogramming the nuclei of differentiated adult cells [12]. Many of the early reports used bone marrow as a source of stem cells, but other sources of mesenchymal stem cells (MSC) have been more recently demonstrated. For example muscle, teeth, cartilage, hair, adipose tissue all have been shown to contain multipotent MSC.

Isolation of MSC from bone marrow or digested tissue extracts is most commonly achieved by simple adhesion and proliferation of MSC to tissue culture surfaces. This crude technique does not ensure a homogenous population of MSC because cells such as fibroblasts may likewise readily adhere and proliferate. While non-progenitor cell contamination may be an expected outcome of the adhesion sorting technique, the extensive volume of literature detailing bulk multipotent behavior of adherent MSC populations demonstrate the presence of a significant, if not a homogenous, MSC population. In fact, near-homogenous MSC populations have been reported from adhesion sorting [13]. Researchers are currently working on more rigorous methods of identifying stem cells through the use of cell surface antigens such as cluster differentiation (CD) factor $CD34^+$, $CD44^+$ and $CD133^+$ cells. There is still significant research to be done in this area, and a consensus on the exact antigen profile of a MSC has not been reached. Most of the research aimed at clinical treatments has been carried out using autologous [14] MSC, mainly from bone marrow. Specifically, bone marrow derived stem cells have been used in vitro to generate bone, cartilage, tendon, ligament, meniscus, intervertebral disc, fat, muscle, and nerve [14]. Because of the availability of adipose tissue, it too has received a fair amount of recent research as a source of MSC [15].

Recently, umbilical cord (UC), dental pulp (DP), and menstrual blood (MB) mesenchymal stem cells have gained much attention because of their convenient harvesting procedures, excellent proliferation and differentiation abilities, less susceptibility to bacterial and viral contamination, and no ethical restrictions [16] . Previous studies have reported the therapeutic potential of these MSCs using various models, such as neurodegenerative disorders [17, 18], rheumatoid arthritis [19], hind limb ischemia [20], and diabetes [21], but no direct comparative studies of those three sources of MSCs have been made so far.

In cardiology, stem cells have emerged as a promising strategy for cardiac replacement or repair after acute myocardial infarction (MI) [22]. From a historical perspective, a brief insightful review article titled- "Reparative Processes in Heart Muscle Following Myocardial Infarction" described the appearance of round cells in the border-zone of acute MI after the surge of acute inflammatory cells but stopped short of explaining or characterizing these cells [23]. Murry and colleagues demonstrated that haematopoietic stem ($CD34^+$, $CD45^+$) cells do not transdifferentiate into cardiac myocytes in myocardial infarcts [24]. Further studies in animal models of MI demonstrated that several subsets of adult primitive cells can regenerate cardiomyocyte with improvement in cardiac function. However, the last 15 years have witnessed an exponential increase in literature about the therapeutic use of stem cells after acute MI. Multiple clinical studies have examined the safety and efficacy of stem cell therapy after acute MI. Majority of the initial clinical trials, although diverse and heterogeneous in their design and execution, have shown that stem cell therapy is safe and leads to, at least, modest improvement of cardiac function. There is ongoing debate on what constitutes the best source of stem for the repair of damaged myocardium following a MI. To date, most of the studies have used autologous stem cells derived from bone marrow and peripheral blood. Studies that have used allogeneic human mesenchymal stem cells (hMSCs) following acute MI have, at least, established the safety profile of allogenic stem cell therapy for clinical use [25, 26]. Newly discovered stem cell types, e.g., resident cardiac stem cells and very small embryonic-like stem cells have been a focus of intense research to further characterize their plasticity [27, 28], homing and growth characteristics, safety and efficacy to repair damaged myocardium and improve cardiac function [26]. Endogenous cardiac stem cells are tissue-specific stem progenitor cells harbored within the adult mammalian heart. They were first discovered in 2003 [29, 30] in the adult rat heart and since then have been identified and isolated from mouse, dog, porcine and human hearts [31, 32].

Heart failure is the leading first cause of death worldwide, and current therapies only delay progression of the disease. Cardiomyocytes are a stable cell population with only limited potential for renewal after injury [33, 34]. Cardiac tissue regeneration may be due to infiltration of stem cells, which differentiate into cardiomyocytes [35]. Laboratory experiments and recent clinical trials suggest that cell-based therapies can improve cardiac function [36, 37], and the implications of this for cardiac regeneration are causing great excitement. These new findings have stimulated optimism that the progression of heart failure can be prevented or even reversed with cell based therapy [38]. In this context, several methods using adult bone marrow cell (BMC) therapy started in the overall the world. Among these, the authors found no effects of intracoronary injection of autologous mononuclear BMC on global left ventricular function [39-43]. In another study, the effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure was assed. Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMCs compared with placebo did not improve left ventricular end-systolic volume (LVESV), maximal oxygen consumption, or reversibility on single-photon emission computed

tomography (SPECT, or less commonly, SPET) [44]. In other study, intracoronary injection of bone marrow-derived mononuclear cells early or late after acute myocardial infarction was analyzed. In this study, among of patients with ST-segment elevation myocardial infarction and left ventricular (LV) dysfunction after successful reperfusion, intracoronary infusion of bone marrow mononuclear cells (BMMNC) at either 5 to 7 days or 3 to 4 weeks after acute myocardial infarction did not improve LV function at 4-month follow-up [45].

Compared with the BMMNC, the $CD133^+$ cell extracted from BMMNC promotes cardiac recovery after recent myocardial infarction [46, 26]. But intra-myocardial injection of $CD133^+$ cell has no effect on global LV function and clinical symptoms [47].

The promising approaches of bone marrow cell therapy was reported by Afzal et al (2015) using database researches through 2014 that they identified in 48 randomized controlled trials enrolling 2602 patients. By this meta-analysis, authors concluded that transplantation of BMC improve LV ejection fraction, reduce infarct size and ameliorates remodeling in patients with ischemic heart disease. BMC transplantation may also reduce the incidence of death, recurrent myocardial infarction; ventricular arythmia and cerebrovascular accident during follow up [48].

In Tajikistan (Table) for the first time the laboratory for investigation of stem cell created in Avicenna Tajik state Medical University, Dushanbe at November 29, 2009 and the first clinical study for heart stem cell therapy started at March 9, 2010. In this study, autologous transplantation of bone marrow derived $CD133^+$ was undertaken with the high degree of success for a cohort of patients with coronary artery disease. $CD133^+$ mesenchymal cells were enriched using magnetic microbed anti-CD133 antibody from bone marrow mononuclear cells. Flow cytometry and immunocytochemistry analysis using specific antibodies revealed that these cells were essentially 89±4% $CD133^+$ and 8±5% $CD34^+$. $CD133^+/CD34^+$ secrete important bioactive proteins such as cardiotrophin-1, angiogenic and neurogenic factors, morphogenetic proteins, and proinflammatory and remodeling factors in vitro [49]. Single intracoronary infusion of autologous $CD133^+/CD34^+$ is effective and reduces infarct size in patients as analyzed by Tc99m MIBI myocardial scintigraphy. Is majority of patients were treated via left coronary artery. Nine months after cell therapy, 5 out of 8 patients showed a net positive response to therapy in different regions of the heart. Uptake of Tc99 isotope and revitalization of the heart area in inferoseptal region are more pronounced ($p= 0.016$) as compared to apex and anterospetal regions after intracoronary injection of the stem cells. The cells chosen here have the properties essential for their potential use in cell therapy. In addition their homing can be followed without major difficulty by the use of scintigraphy. The cell therapy proposed here is safe and should be practiced, as we found, in conjunction with scintigraphic observation of areas of the heart which respond optimally to the infusion of autologous $CD133^+/CD34^+$ BMMNCs [26, 49].

Table *Landmark events in the history of stem cell discovery and its use for the therapy of myocardial ischemia*

Year	Event
1908	A Russian-American scientist – Alexander A. Maximow proposed the term “stem cells”. He stated that all the blood cells have a single precursor cell [10]
1996	Murry and associates sought to redirect heart to form skeletal muscle instead of scar by transferring the myogenic determination gene, MyoD, into cardiac granulation tissue
2001	Shintani et al. reported that lineage-committed endothelial progenitor cells and $CD34^+$ mononuclear cells can be mobilized during an acute ischemic event in humans [Shintani S et al. *Circulation*. 2001;103:45-6]
2002	Assmus et al. reported that intracoronary infusion of autologous blood or bone-marrow progenitor cells is safe and feasible and may benefit post-MI remodeling [Assmus B et al. *Circulation*. 2002;106:3009-17]
2003	Stamm et al. injected autologous $CD133^+$ bone-marrow cells into the infarct border zone and suggested an improvement of myocardial perfusion is likely [42]
2003	Menasche et al. reported that autologous skeletal myoblast transplantation for severe ischemic cardiomyopathy can improve regional contractility but might have arrythmogenic potential [Menasche P et al. *JACC*. 2003;41(7):1078-83]
2003	Beltrami et al. reported that adult cardiac stem cells are multipotent and support myocardial regeneration [29]
2004	Kucia et al. reported very small nonhematopoietic population of bone marrow-derived cells that express markers for cardiac differentiation [41]
2004	Kang et al. injected G-CSF for the mobilization of PBSCs and administered these cells via intracoronary route to heart after MI. Although improvement of cardiac function was noted, a significant concern was raised for the possibility of coronary restenosis after stem cell therapy [40]
2009	Hare et al. provided safety and provisional efficacy data for allogeneic human mesenchymal stem cells in MI patients [25]
2010	March 9, the first clinical study for heart stem cell therapy started in Avicenna Tajik State Medical University, Dushanbe, Tajikistan
2011	The first randomized and open-labeled phase I clinical study utilizing intracoronary injection of resident CSCs in patients with a history Q-wave MI and EF<40% started recruiting patients [28].
2012	Stem cell scientists awarded Nobel Prize in Physiology and Medicine. In what researchers view as validation of the field, the Nobel committee recognized pioneering contributions to stem cell science by John Gurdon and Shinya Yamanaka
2013	The first results of Tajik clinical study for heart stem cell therapy published [26]

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