

# Stem Cell and Stem Cell Therapy in Thailand

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**ABSTRACT:** Stem cells have the properties of unlimited self renewal and differentiation into various cells or tissues. Stem cells can be divided into embryonic and adult stem cells. Embryonic stem cells can differentiate into all kinds of tissues or are pluripotent, whereas adult stem cells can differentiate into many but not all kinds of cells, and are multipotent. Hematopoietic stem cells have long been used to cure several hematologic disorders. The successful isolation and culture of human embryonic stem cell for the first time in 1998 generated the new hope of using stem cells for therapy of several diseases especially degenerative disorders, traumatic organ damage and aging. Human embryonic stem cells have been extensively investigated; however, clinical trials in human are not yet feasible and ethical problems exist. Adult stem cells especially hematopoietic stem cells are being used to treat several diseases in pilot and randomized controlled trials; further research, both basic and clinical, are however required in order to understand the mechanisms and the effectiveness of stem cell therapy. Of the most importance is to develop regulation and guideline for stem cell therapy especially human clinical trials as well as to provide public and physician education.

**KEYWORDS:** Stem cell therapy, hematopoietic stem cells, embryonic stem cells, clinical trials.

## INTRODUCTION

The first isolation and successful culture of human embryonic stem cells by Thomson, *et al* in 1998 has led to the hope of using stem cell therapy to restore the function of organs or tissues. Since then, there has been an enormous explosion of research in this field, on the possibility of cell-based therapy to treat several diseases, and regenerative or reparative medicine. However, research work on embryonic stem cells were retarded because of ethical concerns. Scientists therefore turned their interest to adult stem cells instead. Adult stem cells of the hematopoietic system or hematopoietic stem cells (HSC) have been known to scientists for many years and are being used as standard therapy for several hematological disorders. The potential application of stem cell therapy to diseases other than hematological disorders, or the new generation of stem cell therapy includes ischemic heart disease, ischemic cardiomyopathy, stroke, Parkinsonism, motor neuron disease, diabetes, liver failure, cancer, and bone and cartilage disorders.

## HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THAILAND

Hematopoietic stem cell transplantation (HSCT) was first performed in Thailand in June 1986 at Siriraj Hospital, Mahidol University, where the Chulabhorn Bone Marrow Transplant Center was established later in 1988, under the initiation and support of Professor

Dr. H.R.H. Princess Chulabhorn I. At present, there are 3 other bone marrow transplant units, including those at Ramathibodi Hospital Mahidol University, Chulalongkorn Hospital, and Pramongkutklao hospitals.

HSCT is so far the therapy of choice for several hematological diseases, malignancies and immune disorders. In Thailand, hematological malignancies and other hematologic disorders are prevalent. Hematological malignancies including acute leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma and multiple myeloma are as common as in Western countries. The incidence of aplastic anemia is at least twice more common than in Europe and the U.S.A. Severe thalassemia including homozygous  $\beta$ -thalassemia and Hb E/ $\beta$ -thalassemia are frequently found in Thailand. HSCT can therefore benefit patients with hematological malignancies, aplastic anemia and thalassemia. Approximately 120-150 patients are being transplanted in Thailand annually. About half are allogeneic and the rest are autologous. The sources of HSC are bone marrow, mobilized peripheral blood, and cord blood. The overall results are more or less equal to the results reported from the Western countries. The long term disease free survival is approximately 60-70%<sup>2</sup>. The incidence of acute GvHD is low, approximately 15-20%. Acute GvHD more than grade II occurs at less than 10%. Chronic GvHD is more common among those who undergo peripheral blood stem cell transplantation.

The results of HSCT for thalassemia are favorable

when the patients undergo the procedure as early as possible<sup>3</sup>. Nearly 90% of patients with class I and class II can be cured. However, in those with class III or with severe manifestations or in adult patients, the results are poor with high rate of recurrence of the disease. In this population, several attempts are being used to overcome the problem of graft rejection or graft failure. Those include the use of hypertransfusion, and adequate iron chelation prior to transplantation. Modified conditioning regimens have been used in order to eradicate the residual thalassemic clone<sup>3</sup>. Reduced intensity HSCT has been reported to be successful in this group of patients; however, the numbers are too small<sup>4</sup>.

In many families in which the first child has thalassemia, the parents are afraid of having another thalassemia baby. However, with prenatal diagnosis, it is feasible to have an unaffected child, and also HLA typing can be performed. If HLA is compatible with the first affected child, cord blood can be collected at birth and used to cure the older brother. We first reported the success of sibling cord blood transplantation in severe thalassemia in 1995<sup>5</sup>. Up to the present, 20 patients underwent sibling cord blood transplantation at Siriraj Hospital, Mahidol University. The results depended on the patients' status at the time of the transplant and the number of cord blood cells collected. However, the hematological recovery is delayed, especially platelet recovery.

Only 25% of the patients have a HLA-identical sibling as a donor. Donors other than HLA-identical siblings include unrelated HSC donor from national HSC registry and unrelated cord blood stem cell from public cord blood bank. HSCT using a haploidentical donor such as parents, children and sibling are being investigated. If it is successful, every patient who requires HSCT can undergo the procedure. Several measures are being used to overcome the immunological barrier, including the combination of bone marrow and mobilized peripheral blood stem cells<sup>6</sup>. The use of megadoses of mobilized peripheral blood cells depleted for CD 3 and CD 19 which contain large number of HSC (CD 34+ and CD 34-) and natural killer cells has provided the favorable results in haploidentical transplantation<sup>7</sup>.

HSCT is expensive, costing approximately US\$ 25,000, although this is much cheaper than in the West. Therefore, not all eligible patients can afford this therapy.

## A NEW GENERATION OF STEM CELL THERAPY

Embryonic stem cells (ESC) are the most promising source for replacement therapy because ESC can be grown indefinitely in culture, can be genetically manipulated, and can be differentiated to specific

tissues by using specific differentiation protocol. Similar to adult stem cells, allogeneic ESC-based therapy is feasible only with HLA-match between the patient and ESC. Therefore, patient-specific ESC are being developed in order to avoid this problem<sup>8</sup>. Those methodologies include nuclear transfer or therapeutic cloning, cell fusion, transduction with defined factors and parthenogenesis, however they are not yet feasible in humans. In order to overcome ethical issues, Human ESC can be derived from a single blastomere, so that the rest of blastocyst can further develop<sup>9</sup>.

With the limitations of ESC, scientists are interested in using adult stem cells as an alternative source for stem cell therapy. HSC from the bone marrow, mobilized peripheral blood and cord blood have been extensively studied and used to treat hematological disorders. Previous studies show the evidence that adult stem cell plasticity exists, e.g. HSC can differentiate into neuronal cells and myocardial cells. Recent evidence did not confirm this finding or if adult stem cell plasticity exists, it is not efficient enough to repair or restore the damaged tissues or organs. Autologous adult stem cells can be used; therefore, there is no immunological problem, which is the advantage of adult stem cell therapy.

Attempts have been made to isolate and culture adult stem cells to be cells with pluripotent property similar to ESC. Multipotent adult progenitor cells have been reported to be isolated after several passages; however, it was found to be not reproducible later on. Recently, amniotic fluid stem cells have been isolated and were found to have pluripotent property<sup>10</sup>.

## CLINICAL TRIALS OF STEM CELL THERAPY

The first human ESC trial will be performed in patients with spinal cord injury in the near future. There are several clinical trials using adult stem cells in several diseases including ischemic heart diseases, CNS disorders, diabetes, diabetic ulcer and osteoarthritis. Most studies are pilot studies with only small numbers of patients, so they are therefore not conclusive. Extensive studies of HSC therapy for ischemic heart diseases have been performed<sup>11</sup>. The cell sources were from bone marrow or mobilized peripheral blood, either mononuclear cell fraction or purified CD34+ or CD133+. The methods of cell delivery were varied including intravenous infusion, intracoronary arterial injection or direct injection into ventricular wall. In some studies, they used growth factor injection to mobilize stem cells from the bone marrow into peripheral blood so that the high number of mobilized HSC will go to the injury sites. The results in randomized controlled trials reveal inconsistency, with marginal and unsustainable improvement.

In Thailand, several trials, mostly pilot studies, are being carried out in patients with ischemic heart disease, stroke, motor neuron disease, diabetic ulcer osteoarthritis in university and private hospitals. In some private hospitals, a special program is offered to the patients to have stem cell therapy abroad. Also, animal stem cells are also used for stem cell therapy.

Autologous stem cells can be collected and stored for further therapy in the future. These include cord blood stem cells and mobilized peripheral blood stem cells. Based on experiences in the U.S.A., the benefit is very limited, because only HSC transplant is the standard treatment, and autologous HSC transplant can be effectively performed in only small numbers of hematological diseases.

Stem cell therapy is at present the standard treatment for hematological disorders. For other diseases, it is still under investigation. Therefore, scientists have to do more basic and clinical research to better understand the diseases and the mechanisms of how stem cells work. William Oster stated that "The transition from popgun pharmacy to targeted therapy first requires a firm understanding of the pathophysiological basis of the desired therapeutic end point". The field of stem cell research is complex requiring the harmonization of science, education, policy and business. Public and physician education, as well as the development of regulation and guideline for human stem cell therapy, are badly needed, particularly for Thailand.

International collaboration among scientists in Asia-Pacific region have been initiated. Recently, scientists from several countries including Australia, China, India, Japan, South Korea, Singapore, Taiwan, and Thailand came to meet and agreed to establish a stem cell network for the Asia Pacific region (SNAP). The mission of the network is to promote stem cell research in the region, to provide the education and training for students and young scientists and to develop scientific and ethical guidelines. With SNAP, we scientists in Asia-Pacific region wish to have close and further collaborations in the field of stem cell research, with the ultimate goal of providing benefit to the mankind.

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