

## **Introduction & Aim of the work**

Over the last couple of decades allogeneic bone marrow transplantation was accepted as a therapy for a variety of hematological malignancies, bone marrow failure syndromes, immunodeficiency states and metabolic disorders (*Wagner et al, 1995*)

However, allogeneic bone marrow transplantation is limited by the availability of suitable HLA-compatible donors, risk of graft versus host rejection & risk of opportunistic infection . (*Wagner et al, 1995* )

Studies of the regenerating hematopoietic system have led to the definition of many of the fundamental principles of stem cell biology. (*Daly, et al, 2003*).

Therapies based on a range of tissue stem cells have been widely touted as a new treatment modality, stem cells from embryonic and somatic sources to provide replacement cell therapies for genetic, malignant, and degenerative conditions. (*Daly, et al, 2003*).

There have been also many trials for stem cell use in advanced breast carcinoma, liver diseases (in animal model) & neurological disease, . (*Margot et al, 2003*)

Recently there has been new interest for the use of stem cell therapy in cardiac diseases as coronary artery disease, congestive heart failure, cardiomyopathy & severe angina. .  
(*Margot et al, 2003*)

Although most of these trials have been carried on small group of patients, they gave very promising results. (*Margot et al, 2003*)

The body has natural way to regenerate itself, and the cardiovascular system is a part of it .Angiogenic cell precursors (ACPs) originates in the bone marrow and then circulates in the blood vessels play the major role. (*Fulga et al, 2005*)

The VesCell is manufactured from small quantity of (ACPs) from blood and injected directly through a special technique into the heart muscle, and then it starts to regenerate special parts of the muscle. (*Fulga et al, 2005*)

VesCell uses patients` own adult stem cells to treat heart disease and is a viable therapeutic possibility for heart patients without any other treatment option. (*Fulga et al, 2005*)

## **Aim of the study**

Write in details all information available on the use of stem cell in cardiac diseases to be able to assess its possible use clinically for treating cardiac diseases which are incurable by other forms of treatment

## **Methods**

Search on all possible articles in the libraries and medical websites.

# **Stem cell therapy in cardiac disease**

## ***Essay***

*Submitted for Partial Fulfillment of master degree of  
Clinical Hematology*

***Presented by***

**Rasha Galal Ali Ahmed**

*M. B. B. Ch.  
Faculty of Medicine  
Ain Shams University*

***Under Supervision of***

**Prof. Dr.Maha El-Zimaity**

***Prof. of Clinical Hematology  
Faculty of Medicine - Ain Shams University***

**Dr. Samar Mohammed Refa'at**

***Dr.lecturer of clinical hematology  
Faculty of Medicine - Ain Shams University***

**Dr.Ghada Metwally Tawfick El-Gohary**

***Dr.lecturer of clinical hematology  
Faculty of Medicine - Ain Shams University***

**Faculty of Medicine**

**Ain Shams University**

**2006**

## References

Margot S.Kruskall, MD, Anna Merino, MD, PhD: The Journal of American Association of Blood Banks, The mesenchymal stem cell revealed, Transfusion Vol.43, No.1, january2003:1.

Wanger JE, Kernan NA, Steinbuch M, Broxmeyer HE and Gluckman E (1995): Allogeneic sibling umbilical cord blood transplantation in children with malignant and non malignant diseases .Stem cell transplantation. Lancet 346: 214-219.

Valentine Fulga,MD ,CEO of TheraVietae,David Czeiger,MD,medical director of TheraVietae,VesCell a natural treatment for heart disease,RedOrbet.November 16,2005.

Serdar Bedii Omay, MD,Stem cell therapeutic applications and production technology "Turkish experience",stem cell technology,insights and applications.February 07,2006.

Galmes A,Besalduch Z,Baragy Z,Matamoros N,Duran MA,Morey M ,Alvarez F and Mascaro M (1996):Cryo preservation of heamatopoietic progenitor cells with 5%dimethyl sulfoxide al 80 degrees c without rate controlled freezing. Transfusion 36:797.

George Q. Daley, Margaret A. Goodell and Evan Y. Snyder.Realistic Prospects for Stem Cell Therapeutics.the American society of heamatology.2003.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145–1147.

Doetschman TC, Eistetter H, Katz M, Schmidt W, Kemler R. The in vitro development of blastocyst-derived embryonic stem cell lines: formation of visceral yolk sac, blood islands and myocardium. *J Embryol Exp Morphol.* 1985;87:27–45.

Ding S, Wu TY, Brinker A, et al. Synthetic small molecules that control stem cell fate. *Proc Natl Acad Sci U S A.* 2003;100:7632–7637.

He JQ, Ma Y, Lee Y, Thomson JA, Kamp TJ. Human embryonic stem cells develop into multiple types of cardiac myocytes. action potential characterization. *Circ Res.* 2003;5:5.

## المقدمة

تعتبر عملية زرع نخاع العظم علي مرالعقدين الماضيين من أهم الطرق لإنقاذ المرضى من تأثير الإشعاعات القاتلة والكثير من أورام الدم والعلاج الكيماوي علي الدم وأيضا حالات نقص المناعة وبعض حالات الخلل فى العمليات الأيضية.

ويتم الحصول علي نخاع العظم من المريض نفسه أو من متبرع مطابق له من حيث نوع الخلايا لتجنب المضاعفات الخطيرة كالعوى المتكررة وتفاعل خلايا المتبرع ضد خلايا المريض .

وتشير الكثير من الدراسات إلى القدرة الذاتية لتجديد خلايا الدم مما أدى إلى توجيه الأنظار إلى خلايا الدم الأم الجذعية كوسيلة لعلاج الكثير من لمرضى.

ويعتبر هذا النوع من العلاج من أحدث الطرق المبتكرة حيث يتم الحصول على الخلايا الجذعية من دم الحبل السرى للأجنة أو من نخاع العظم للمريض نفسه.

وقد تم في الآونة الأخيرة الكثير من المحاولات لعلاج حالات سرطان الثدي وبعض أمراض الكبد ( تجارب علي الحيوانات ) وبعض الأمراض العصبية عن طريق خلايا الدم الأم الجذعية .

لقد زاد الاهتمام بخلايا الدم الأم الجذعية في علاج الكثير من أمراض القلب كانسداد الشريان التاجي وفشل القلب الإحتقاني وضعف عضلة القلب و الذبحة الصدرية الشديدة .

وبرغم قلة عدد المرضى الذين خضعوا لهذا النوع من العلاج إلا أنها أعطت نتائج مذهلة.

إن هذه العملية ببساطة تتم عن طريق الحصول على هذه الخلايا وحقنها مباشرة فى الأجزاء الميتة من عضلة القلب لتبدأ الخلايا بتجديد نفسها.

يعتبر هذا النوع من العلاج الحل الوحيد للكثير من المرضى الذين لا يوجد لحالاتهم أى حلول أخرى و ذلك عن طريق خلاياهم الخاصة.

### الهدف من الدراسة:

تجميع كل المعلومات الجديدة عن استخدام خلايا الدم الأم الجذعية فى علاج مرضى القلب.

# استخدام خلايا الدم الأم الجذعية فى علاج امراض القلب

رسالة مقدمة من

طبيبة/رشا جلال على أحمد

بكالوريوس الطب و الجراحة – جامعة عين شمس

توطئة للحصول على درجة الماجستير فى أمراض الدم الإكلينيكية

تحت إشراف

الأستاذة الدكتورة/مها الزميتى

استاذ أمراض الدم الإكلينيكية

كلية الطب/جامعة عين شمس

مدرس/سمر محمد رفعت

مدرس أمراض الدم الإكلينيكية

كلية الطب/جامعة عين شمس

مدرس/غادة متولى توفيق الجوهري

مدرس أمراض الدم الإكلينيكية

كلية الطب/جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠٠٦



## **Abstract**

The mesenchymal stem cells have a great therapeutic potential due to its ability to self renewal and differentiation into many types of specialized cells.

This character initiated the idea of using stem cells in treatment of many diseases related to permanent damage of the tissues such as cardiac diseases.

Over the past few years some experiments on animals revealed the success of the theory, and many human cases reported to be healthy after a myocardial infarction followed by stem cell therapy.

In this research we will try to spotlight the main characters of stem cell, its sources, how to increase its number and the modality of treatment of cardiac diseases by stem cells.

## Index

Title	Page Number
List of appreviations .....	1
List of tables.....	3
List of figures.....	4
Abstract .....	5
Introduction and Aim of the work.....	6
Chapter 1 Hematopoitic stem cell.....	10
Chapter 2 Stem cell plasticity.....	26
Chapter 3 Bone marrow derived cardiomyocytes.....	35
Chapter 4 Stem cell sources for cardiac therapy.....	40
Chapter 5 Collection of Peripheral Blood Progenitor Cells (PBPC).....	47
Chapter 6 Experimental studies.....	69
Chapter 7 Cardiac Therapy by Stem Cells.....	82
Summary .....	96
References .....	100

## List of abbreviations

<b>ANC</b>	Absolute Neutrophil Count
<b>ACPs</b>	Angiogenic Cell Precursors
<b>BMT</b>	Bone Marrow Transplantation,
<b>CD</b>	Cluster of Differentiation
<b>CFU-S</b>	Colony Forming Unit in the Spleen
<b>CFU-GM</b>	Colony-Forming Unit-Granulocyte-Macrophage
<b>CBC</b>	Complete Blood Count
<b>CABG</b>	Coronary Artery Bypass Graft
<b>FISH</b>	Fluorescence In Situ Hybridization
<b>G-CSF</b>	Granulocyte-Colony Stimulating Factor
<b>GM-CSF</b>	Granulocyte-Macrophage Colony Stimulating Factor
<b>HGFs</b>	Hematopoietic Growth Factors
<b>HSC</b>	Hematopoietic Stem Cell
<b>HLA</b>	Human Leukocyte Antigen
<b>ID</b>	Identification
<b>IRV</b>	Interstitial Retrograde Coronary Venous
<b>IC</b>	Intracoronary
<b>IM</b>	Intramyocardial
<b>I.V</b>	Intravenously
<b>LVL</b>	Large Volume Leukapheresis
<b>L.V</b>	Left Ventricle
<b>LVEF</b>	Left-Ventricular Ejection Fraction
<b>MSCs</b>	Mesenchymal Stem Cells
<b>MCE</b>	Myocardial contrast echocardiography

<b>PBSC</b>	Peripheral Blood Stem Cells
<b>PBMNCs</b>	Peripheral Blood Mononuclear Cells
<b>PBPC</b>	Peripheral Blood Progenitor Cells
<b>rhG-CSF</b>	recombinant human Granulocyte-Colony Stimulating Factor
<b>RBCs</b>	Red Blood Cells
<b>SP</b>	Side Population
<b>TH2</b>	T-Helper lymphocyte type 2
<b>WBCs</b>	White Blood Cells

## List of figures

Figure	Title	Page Number
Figure1	differentiation of stem cell	12
Figure2	development of stem cell	15
Figure3	Fluorescent markers can be used to identify stem cells hidden among ordinary adult cells	23
Figure4	stem cell culture	44
Figure5	Rodent Model of Myocardial Infarction	76
Figure6	Heart Muscle Repair with Adult Stem Cells	77

**List of tables**

Table	Title	Page Number
Table1	Proposed cell-surface markers of undifferentiated hematopoietic stem cells	25
Table2	cellular characters of each type of stem cells used in autologous transfusion	46
Table3	Comparing BM to PBSC collection from donors	56

## Acknowledgments

First of all thank Allah for granting me the ability to complete this work till it came to an end.

I would like to express my deep gratitude and cordial appreciation to **Prof.Dr.Maha El-Zimaity** professor of Clinical Hematology, Faculty of Medicine- Ain Shams University for her continuous encouragement and intensive unlimited support.

I would also like to express my gratitude to the continuous help and care offered to me by **Dr. Samar Mohammed Refa'at**, lecturer of clinical hematology Faculty of Medicine - Ain Shams University

With my deep appreciation and gratitude to the fascinating effort and expert advice offered to me by **Dr.Ghada Metwally Tawfick El-Gohary**, lecturer of clinical hematology Faculty of Medicine - Ain Shams University, in every step of this work.

Lastly no words could even express my deepest gratitude to my father, my mother, and my husband, their favor is unforgettable.