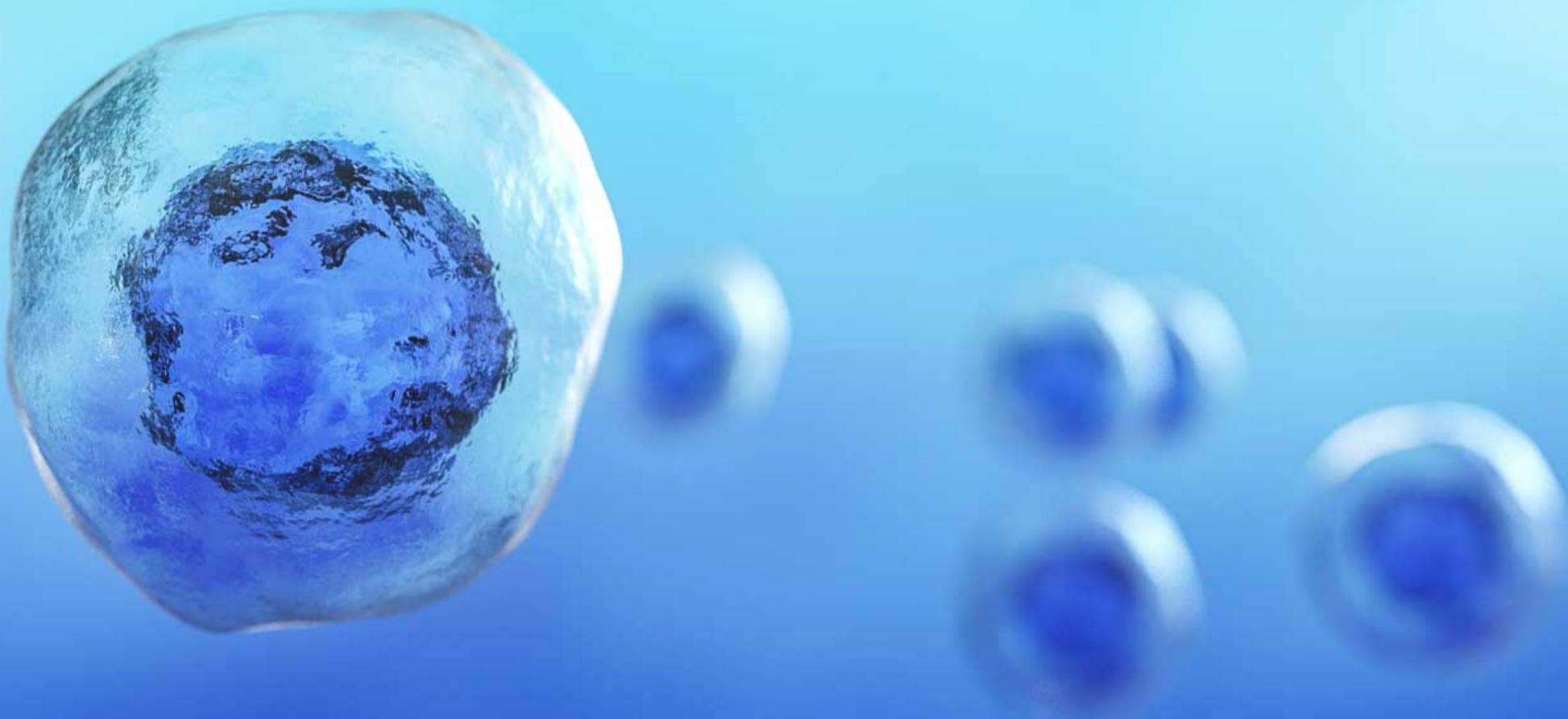


*evidence based practice*

# STEM CELL THERAPY

---

REVIVAL CLINIC BANGKOK



# PREFACE

---

Revival Clinic and Dr. Chontirov would like to give our patient family a small gift of knowledge.

Stem cell therapy is a therapeutic method that when done correctly and safely, will give amazing measurable results. We have seen and witnessed firsthand, numerous borderline miracles from this treatment. stem cells treatment. As with most strategies of treatment, the key here is the earlier the treatment, the better the result. We have had numerous individuals who have commented on how they had wished they knew about Stem Cells before.

This book is aiming to fill the gap and provide you with firsthand knowledge. If you spend a short time reading this, the reward will be great. The knowledge you gain may improve the quality of life of yourself or a loved one. Knowledge is priceless.

In this age stress has become a norm. We compete to be better and more successful than others, invest in Brandname items, purchase high end products, only to work harder to cover these costs. Seldom do we think what this does to our bodies mentally and physically.

The right knowledge and discipline are the most important factors for preventive medicine. Not everything is all about money. Inside this book you will also find how to live a proactive, healthy lifestyle to take care of your body.

If we can save a person from ongoing kidney damage and prevent dialysis, we have already saved enormous amounts economically for that family, as well as having improved their longevity and quality of life. If we can treat painful osteoarthritis of the knee without painkillers it means that we save that person from future kidney damage and all the complications from toxic medication. We save their organs. Something that no amount of money or technology can replace with the same quality and function as the original.

This book hopefully will aid in keeping people knowledgeable in what really is the most important, in this rat race to be successful. Our health and the health of our loved ones. The one truly valuable asset we should cherish the most. Life.

Thank you for all your support. Enjoy.

Revival Clinic Team



*About us*

# DR. CHONTIROK

---

Doctor Chontirok Srikasedsarakul is a specialist in Dermatology and Aesthetics. She graduated as a doctor of medicine from Chulalongkorn University in 2008.

Always seeking to expand her knowledge she has furthered her studies attaining a Diploma in Dermatology and Dermatosurgery from the Skin Institute of Thailand and receiving a Diplomate certification from the American board of Anti-Aging Medicine. Extending her understand of skin she completed a Certificate in Primary Skin Care, Cancer Medicine from the University of Queensland, Australia.

Although her primary focus has always been the skin she did not ignore complementary fields, for example, studying hair loss and hair transplant in a Fellowship in Hair Restoration program and most recently has been awarded a Genetics and Genomics Certificate from Stanford University.



# REVIVAL CLINIC

---

Indulge in the next evolution of treatment experience at Revival Clinic Bangkok. World-class expertise with local flavors, set in a tranquil environment to deliver a bespoke experience that is undeniably unique for every guest. We listen to your specific requests and concerns to provide a level of personalized service that is unmatched. From the moment you make your appointment, each step of your time with us will be tailored to you.

Your safety is of paramount importance to us thus our doctors follow the latest industry standards in every stage of your procedure, from the consultation through medication preparation to the administration of the treatment and even on into after treatment care.

Also we only use the most advanced imported medications and medical equipment, to make sure that you get the best effect while maintaining high levels of safety.

---

# CHAPTER 1

---

**WHAT ARE STEM CELLS ?**

---

# WHAT ARE STEM CELLS?

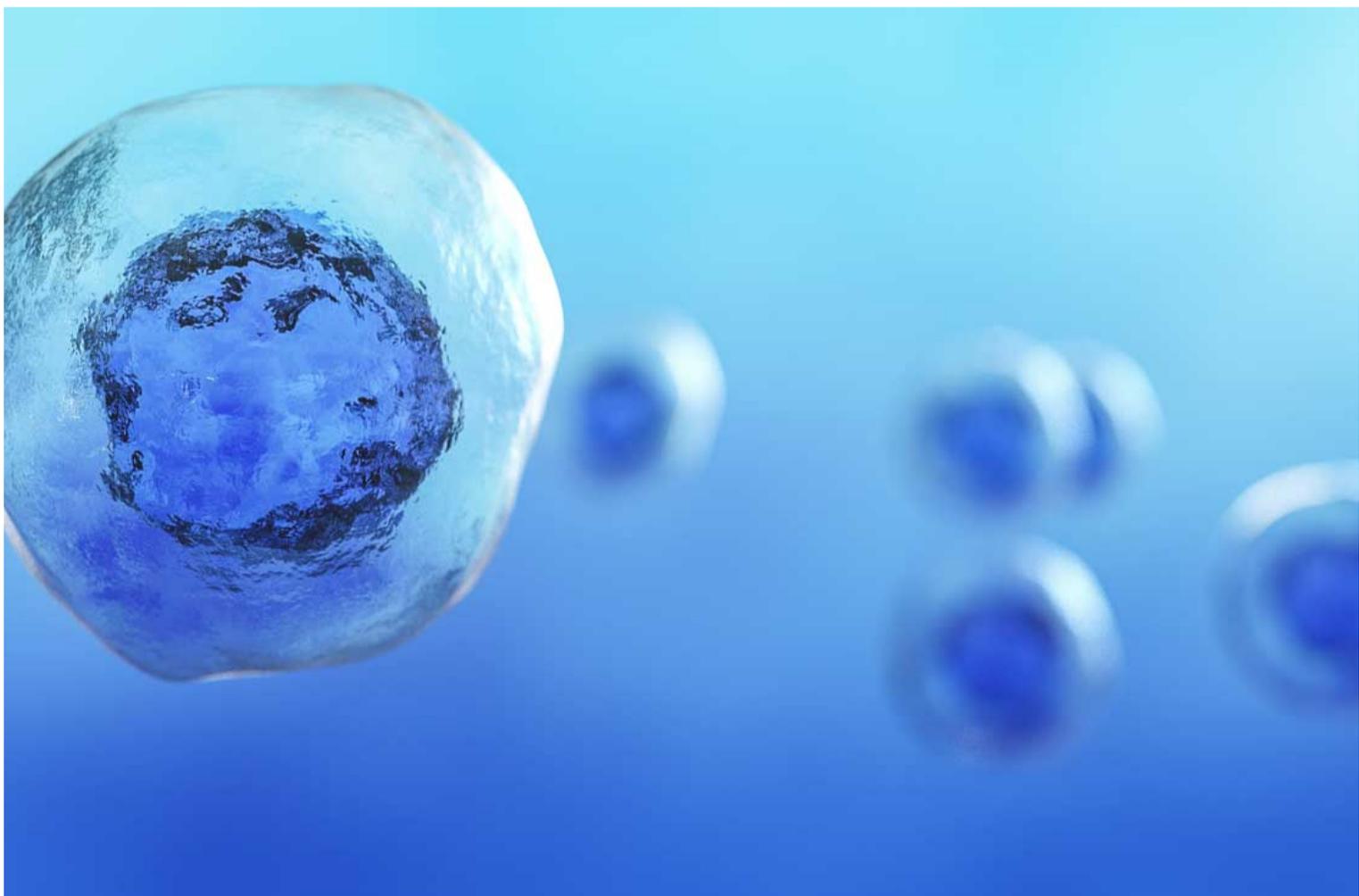
---

Stem cells are distinctive human cells that have the ability to develop into many varieties of cell types, from intestine cells to heart cells. In some manifestations, they also have the potential to repair damaged tissues. [1]

## **IMPORTANCE OF STEM CELLS.**

Stem cells are crucial for living thing for many purposes. In the 3-5 days old embryo, known as a blastocyst, the inner cells generate the whole body of the organism, which include all of the many specialised cell types and part of the body such as the heart, liver, skin, lung, eggs sperm and other tissues. In some adult tissues, such as brain , bone marrow, and brain, separate populations of adult stem cells promote replacements for cells that are broken or death through normal injury, wear and tear, or disease.

Given their special regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, OA knee and heart disease. [2]



# THERE ARE THREE TYPES OF STEM CELLS:

## 1. ADULT STEM CELLS (ASCS)

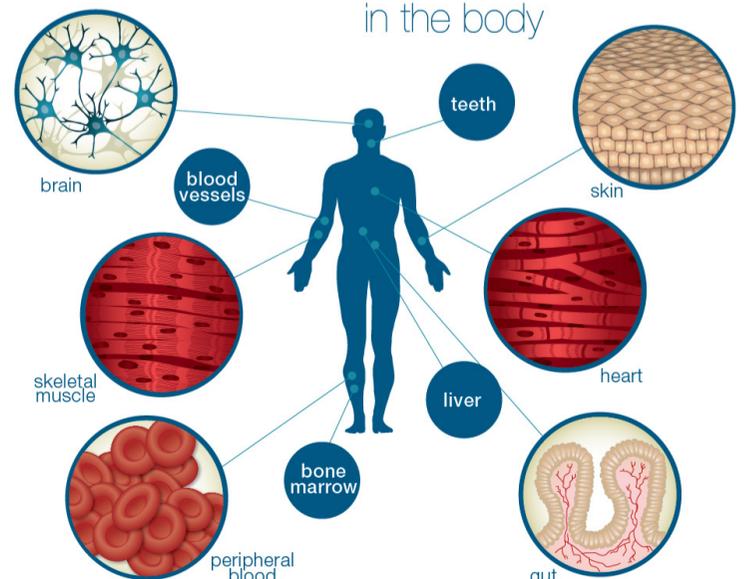
ASCs are un-transformed cells found living within specific differentiated tissues in our bodies that can renew themselves or generate brand new cells that can fill up dead or damaged tissue. You may as well see the name "somatic stem cell" used to refer to adult stem cells. The term "somatic" refers to non-progenitor cells in the body (sperms or eggs). ASCs are typically scanty in native tissues which have rendered them difficult to study and extract for research basics.

Occupier in most tissues of the human body, discrete populations of ASCs generate cells to put back those that are lost through normal repair, injury, or disease. ASCs are found throughout one's lifetime in tissues such as the bone marrow, placenta, umbilical cord, gut, skin, fat tissue, brain, muscle, etc. The first ASCs were extracted and used for blood producing in 1948. This procedure was expanded in 1968 when the first adult bone marrow cells were used in clinical treatment for blood disease.

### *Types of Adult Stem Cells:*

- Mesenchymal Stem Cells
- Neural Stem Cells
- Skin Stem Cells
- Epithelial Stem Cells
- Hematopoietic Stem Cells (Blood Stem Cells)

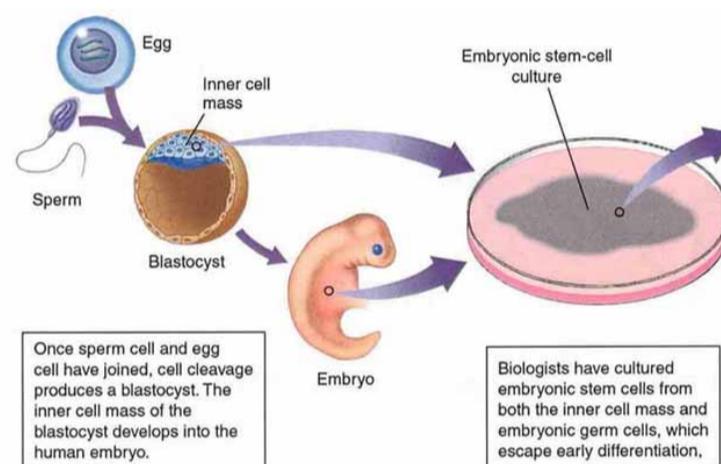
Locations of **Somatic Stem Cells** in the body



## 2. EMBRYONIC STEM CELLS (ESCS)

During days 3-5 after fertilization and prior to implantation, the embryo (at this stage, called a blastocyst), carries an inner cell mass that is capable of generating all the specialized tissues that building the human body. ESCs are obtain from the inner cell mass of an embryo that has been fertilized laboratory and give for research purposes following informed consent. ESCs are not obtain from eggs fertilized in a woman's body.

These pluripotent stem cells, cells that are known to develop into cells and tissues of the three primary germ layers which have the ability to become almost any cell type and are only found during the early phrase of development.



### *Tumor formation from Embryogenic stem cells.*

When implanted into immunocompromised mice, human embryonic stem cells (hESCs) give rise to teratoma, a tumor made up of several different types of tissue, such as hair, muscle, bone, or teeth. The ability to form teratoma is a requisite typical of pluripotent stem cells. [5]

### *Comparison of Different Types of Stem Cells [4]*

	<i>Adult stem cells that form mineralized tissues</i>	<i>Embryonic stem cells</i>	<i>Induced pluripotent stem cells</i>
Derivation	Tissue-specific protocols from different tissues	Inner cell mass of the blastocyst	By viral transduction, or plasmids, or small molecules, or mRNAs of adult cells
Advantages	Moderate division, commitment to specific cell types, can be autologous	Unlimited division, pluripotent, no molecular alteration	Unlimited division (?), pluripotent, no destruction of a blastocyst, autologous
Disadvantages	May not be able to generate enough cells needed for therapy, may take too long to generate cells	Destruction of embryo, incomplete differentiation, possibility of teratoma, allogeneic	Viral integration, equivalence to hESCs (?), genetic memory, incomplete differentiation, possibility of teratoma

## *The similarities and dissimilarity between adult stem cell and embryonic?*

Human embryonic and adult stem cells each have upside and downside regarding potential use for cell-based regenerative treatment. One major difference between adult and embryonic stem cells is their different potential in the number and varieties of differentiated cell types they can become. Embryonic stem cells can suit all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into divergent cell types of their tissue of beginning.

Embryonic stem cells can be grown comparatively easily in culture. Adult stem cells are rare in fully grown tissues, so isolating these cells from an adult tissue is challenging, and technique to expand their numbers in cell culture have not yet been worked out. This is an important distinction, as huge numbers of cells are needed for stem cell replacement treatment.

Scientists think that tissues derived from embryonic and adult stem cells may differ in the chance of being rejected after transplantation. We don't yet know for certain whether tissues obtain from embryonic stem cells would cause transplant rejection, since relatively few clinical study have tested the safety of transplanted cells obtain from embryonic stem cells.

Adult stem cells, and tissues obtain from them, are currently assume less likely to initiate rejection after transplantation. This is because a patient's own cells could be multiplied in culture, coaxed into assuming a specific cell type (differentiation), and then reimplant into the patient. The use of adult stem cells and tissues obtained from the patient's own adult stem cells would mean that the cells are less likely to be turn down by the immune system. This mean a significant advantage, as immune rejection can be circumvented only by continuous giving of immunosuppressive drugs, and the drugs themselves may cause deleterious side effects. [11]

### 3. INDUCED PLURIPOTENT STEM CELLS (IPSCS)

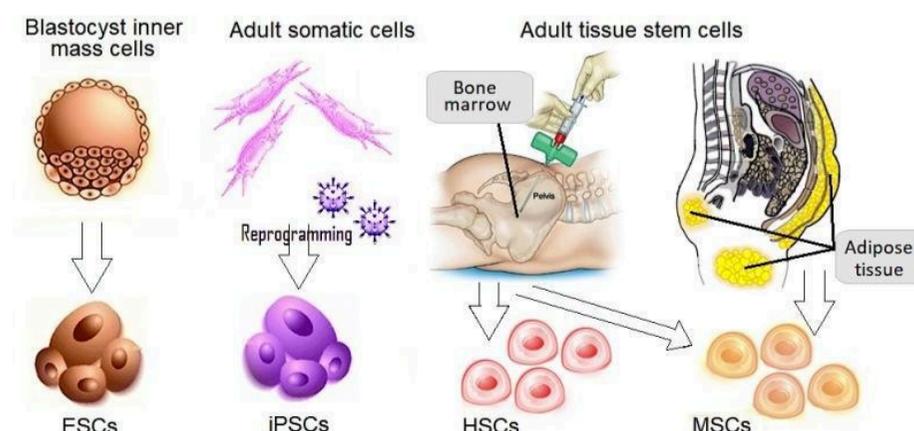
Induced pluripotent stem cells are stem cells that are produced in the laboratory, a middling between adult stem cells and embryonic stem cells. iPSCs are design through the introduction of embryonic genes into a somatic cell (a skin cell for example) that cause it to regress back to a “stem cell like” state. These cells, like ESCs are considered pluripotent invented in 2007, this method of **genetic reprogramming to produce embryonic like cells, is novel and needs many more years of study before use in clinical treatment.** [3]

The original iPS cells were created by using viruses to insert extra copies of three to four genes known to be essential in embryonic stem cells into the specialized cell. It is not yet totally understood how these three to four “reprogramming” genes are able to induce pluripotency; this question is the focus of ongoing study. Furthermore, recent studies have focused on alternative methods of reprogramming cells using methods that are safer for use in clinical settings. [7]

#### *THE PROBLEM OF IPSC PRODUCTION EFFICIENCY AND APPLICATION SAFETY IN CELL TRANSPLANT THERAPY*

Since IPS came from genetic reprogramming technique, another serious problem is the gene set itself that is used for the initiation of pluripotency. The abnormal transcription of cancer gene can lead to tumor development from cells derived from iPSCs, because the expression of cancer gene [a gene which in certain situation can change a cell into a tumor cell

IPSCS is associated with the creating of multiple tumors known in oncogenetics. In particular, the overexpression of cancer gene causes mice outer layer cell change to become cancer, the aberrant expression of Sox2 [cancer gene] causes the development of lump and colon carcinomas, breast tumors.



## *Reference*

- 1.Stanford Children's health "what are stem cells?"
- 2.University of Nebraska Medical Center "The importance of stem cells"
- 3.University of Nebraska Medical Center "Types of Stem Cells"
- 4.Pamela Gehron Robey, Ph.D. Cell sources for bone regeneration The good the bad and the ugly [but promising]. Tissue Engineering Volume 17 November 6, 2011
- 5.Prokhorova TA et al. Teratoma formation by human embryonic stem cells is site dependent and enhanced by the presence of Matrigel. Stem Cells Dev. 2009 Jan-Feb; 18(1):47-54.
- 6.National Cancer Institute, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hematopoietic-stem-cell>
- 7.International Society for Stem Cells Research. Stem Cells Facts

---

# CHAPTER 2

---

## ADULT STEM CELLS & MESENCHYMAL STEM CELLS

---

# THE ADULT STEM CELL IN DEPTH

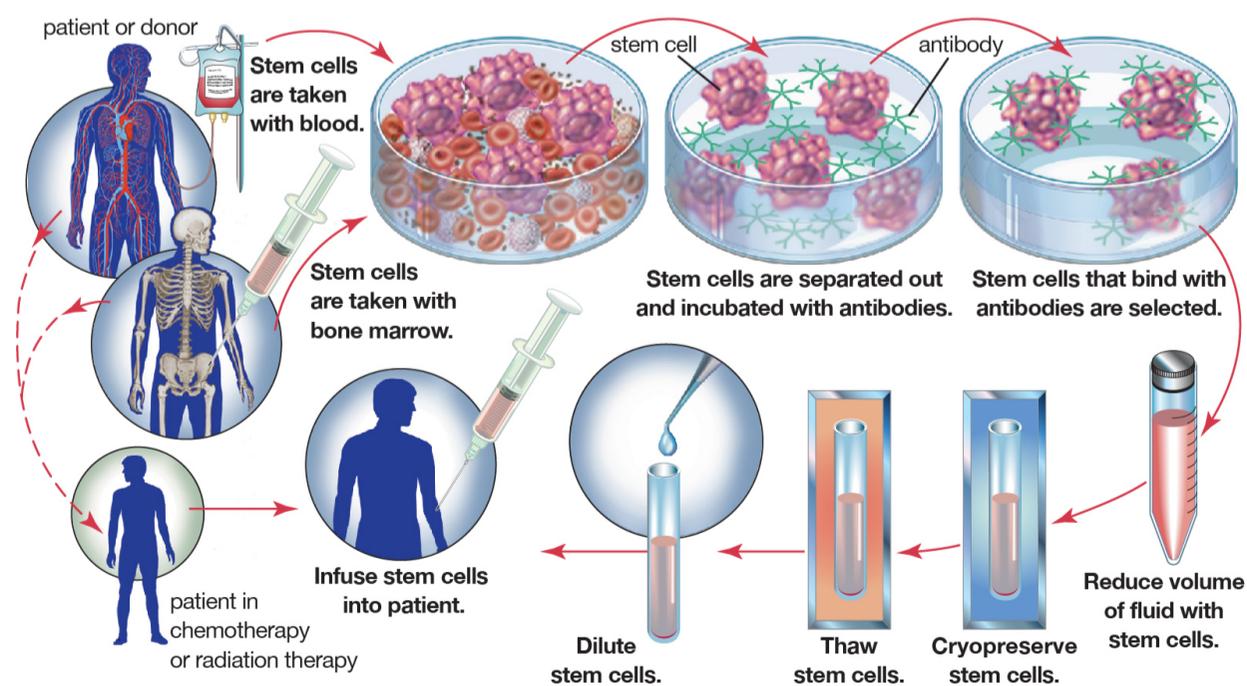
There are many adult stem cells, may be one or more for each tissue of the body. For the sake of brevity, the focus will be on the few that have been widely studied.

## *Neuro-stem cells (NSCs)*

The neuro-stem cells (NSCs) can turn into an amazing array of neurons and neural-related cells such as astrocytes and oligodendrocytes.

## *Hematopoietic stem cell (HSC)*

The longest studied and most clinically related adult stem cell is the hematopoietic stem cell (HSC). HSC is a not fully developed cell that can develop into all types of blood cells, including red blood cells, white blood cells, and platelets. Hematopoietic stem cells are found in the systemic blood and the bone marrow. Also called blood stem cell. [6]



# MESENCHYMAL STEM CELLS

## [MSC]

---

*A stable, safe and highly accessible stem cells.*

Mesenchymal stem cells (MSCs) are adult stem cells which can be extracted from human and animal origin. Human MSCs are the non-haematopoietic, multipotent stem cells with the capacity to become into middle germ cell layer lineage such as adipocytes [fat cell] osteocytes [bone cell], and chondrocytes [cartilage cell] as well neurocytes [nerve cell ] and inner cell layer lineages such as liver cell.

Human- MSCs have been cultured multiple times in specific medium without any severe malformation. Moreover, MSCs have immunomodulatory features, produce cytokines (substances that have an effect on other cells) and immune receptors which regulate the microenvironment in the host tissue. Multilineage potential, balancing immunity and produce of anti-inflammatory molecules makes MSCs an effective implement in the treatment of chronic diseases.

MSCs are present not only in fetal tissues but also in variety adult tissues with few special case. Efficient population of MSCs has been appear from bone marrow. Cells which manifests characteristics of MSCs were isolated from amniotic fluid, adipose tissue, amniotic membrane, endometrium, dental tissues, menstrual blood, limb bud, peripheral blood, fetal membrane and placenta, salivary gland, sub-amniotic umbilical cord lining membrane, skin and foreskin, Wharton's jelly and synovial fluid. [8]

## ADULT STEM CELL PROPERTIES

Stem cells are able to divide and renewing themselves for long periods. All adult stem cells can split into two daughter cells, at least one daughter cell remains as a stem cell.

- Multipotent:** Adult stem cells can turn into a limited number of cell types in a particular cell line.

- The Healer:** Adult stem cells are exquisitely reactive to the composite microenvironment in which they introduced to. Importantly, in injury microenvironments or implantations, the adult stem cells first job with “fixing” the injury before responding to the differentiation requirement of the site or organism. This “sensory” activity is responsive to the phenomenally changing microenvironment of an injury or regenerative site since an injury site clearly goes through essential changes from its start to the final regenerative resolution

- Cell Dominant:** Adult stem cells are the dominant producer in their live cell activities. In clusters of varieties cells in tissues or at sites of injury, their secretory products control or are commanding in the tissue field related to the other cells

- Immuno-Modulator:** All adult stem cells produce molecules that essentially provide a barrier or protector to inhibit all of the interrogators of the immune system from entering an injury or developmental tissue field. This protector or modulatory activity is the first line of shielding against the establishment of autoimmune conditions.

- Provider, Stimulator:** Adult Stem Cells produce bioactive factors that structure both physically and molecularly the injury or developmental (regenerative) functions. The secreted factors contributing to a progressive and dynamically changing microenvironment that supports regenerative activities (not the maintenance of the innervated muscle).

- Regenerative:** Adult stem cells allow regenerative microenvironments and under the appropriate conditions; the end result may be the start of their self-differentiation cascade.

- Homing:** Adult Stem cells has a special ability to “home” to sites of tissue injury, damage, or inflammation

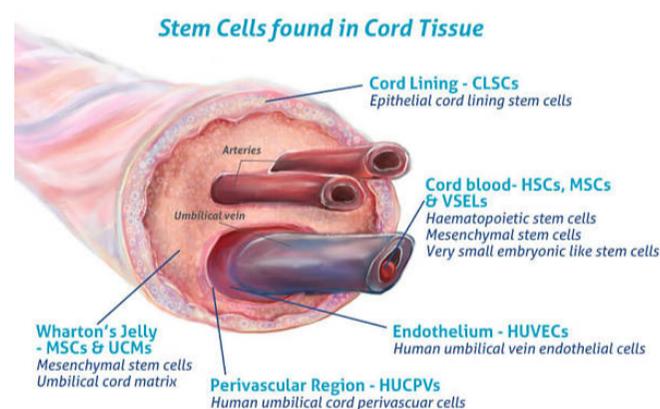
## ADULT STEM CELLS REGENERATIVE ABILITY:

### “THE YOUNGER, THE BETTER “

Adult stem cells, or known as somatic stem cells, are found everywhere in our the body in every tissues and organs after development and function as self-renewing cell pools to refill dying cells and regenerate damaged tissues through our life. Nevertheless, adult stem cells appear to age with the person. As stem cells age, their functional ability also declines. Specifically, this regenerative ability appears to worsen with age, as injuries in older individuals heal more slowly than in childhood. For instance, healing of a fractured bone takes much longer time in elderly than in young individual. There is a considerable amount of evidence showing that deterioration of adult stem cells in the adulthood can become an important player in the start of several diseases in aging such as coronary heart disease, diabetes, Alzheimer, osteoarthritis etc.[9]

## MESENCHYMAL STEM CELLS FROM UMBILICAL CORD.

*‘Among the adult stem cells type Mesenchymal stem cells from umbilical cord are the youngest cell type.’*



Wharton's jelly mesenchymal stem cells (WJ-MSCs) are a type of stem cells with high differentiative ability, an immuno-privileged condition and easy access for extraction. Umbilical cord stem cells offer dominance character over other type of stem cells as a source of therapeutic cells. First, UCM cells are obtain from a noncontroversial, inexhaustible source, and can be collected noninvasively without surgery at low cost. Second, unlike human embryonic stem cells, umbilical cord stem cells did not cause teratomas[tumor].

## Reference

- 1.Sandford Children's health "what are stem cells?"
- 2.University of Nebraska Medical Center "The importance of stem cells"
- 3.University of Nebraska Medical Center "Types of Stem Cells"
- 4.Pamela Gehron Robey, Ph.D. Cell sources for bone regeneration The good the bad and the ugly [but promising]. Tissue Engineering Volume 17 November 6, 2011
- 5.Prokhorova TA et al. Teratoma formation by human embryonic stem cells is site dependent and enhanced by the presence of Matrigel. Stem Cells Dev. 2009 Jan-Feb; 18(1):47-54.
- 6.National Cancer Institute, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hematopoietic-stem-cell>
- 7.International Society for Stem Cells Research. Stem Cells Facts
- 8.Imran Ullah Et Al. Human mesenchymal stem cells - current trends and future prospective. Biosci. Rep. (2015)
- 9.Abu Shufian Ishtiaq Ahmed Et. Al. Effect of aging on stem cells. World J Exp Med 2017 February 20
- 10.Luigi Marino Et Al. Mesenchymal Stem Cells from the Wharton's Jelly of the Human Umbilical Cord: Biological Properties and Therapeutic Potential International Journal of Stem Cells Vol. 12, No. 2, 2019
- 11.National Institute of Health " stem cell basic "

---

# CHAPTER 3

---

## MESENCHYMAL STEM CELLS THERAPEUTIC POTENTIAL

---

# THE THERAPEUTIC POTENTIAL OF MESENCHYMAL STEM CELLS

---

## THE USE OF STEM CELL IN CELLS THERAPY

Cell therapy is the cell transplantation, through local or systemic delivery, of self or other person cells to restore the viability or function of defective tissues.

Medical conditions that may potentially be treated with Mesenchymal stem cells include:

### DEGENERATIVE DISEASE (STEM CELLS FOR ANTI-AGING)

Degenerative disease is a group of wide range disease as a result of process based on wear and tear follow the time goes by. The example of degenerative disease such as Osteoarthritis, Cancer, Alzheimer's disease, diabetes type 2, Muscular dystrophy, Parkinson's disease etc.

As well as our body, stem cells get negative effects from aging too. Scientist believe that the cause of degenerative disease come from aging stem cell which has deteriorate in regenerate potential as a result tissue repairing that use to be done by the healthy stem cells has defect and accumulate to become age-related disease.

Stem cells replacement therapy provides an effective way for the treatment of age-related diseases. It is believed that the regenerative potential of these cells is due to their high proliferation and differentiation capabilities, paracrine activity, and immune privilege.

Somatic stem cell populations differ according to the regenerative needs of the host tissue. In high turnover tissue, such as the gut or hematopoietic system, most stem cell populations are active throughout life. In organs deficient of stem cells, **stem cells transplantation to replace cells** is a promising therapeutic method for functional

recovery. This means that stem cells can be used for cell replacement as a treatment intervention aimed at diminishing the effects of aging. (17)

## **TRAUMATIC SPINAL CORD INJURY**

The use of mesenchymal stem cells (MSCs) constitutes one of the most important and promising treatment approaches. Their favor, among the other sources and types of stem cells such as Embryonic stem cell or IPCCs , increased because of their simplicity of isolation/preservation and their characteristic. The promotion of nerve cells generation or elongation by transplanted neuronal stem cells following damage was reported. (5)



## **STEM CELLS TREATMENT FOR CANCER RECOVERY**

Given their self-renewal and differentiation capacity, stem cells can be used to repair human tissues after chemotherapy. Transplanting HSCs has been broadly clinically utilized to enable lifelong blood cells system recovery after treatment of cancer with high-dose radiation or chemotherapy. This treatment intends to re-establish bone marrow under marrow failure situation (such as aplastic anemia) and to treat congenital blood cell diseases, and works by supplying stem cells that turn into a suitable type of blood cell. Transplantation and successful acceptance of only one HSC can reconstitute blood cells system in recipients.

Healthy stem cells derived can theoretically be utilize to rapair tumor- or treatment-injured tissues. In regenerative medicine, various tissues can be produced using stem cells. Stem cells therapy may be useful in repairing or replacing cancer patient stem cells.(18)

## **STEM CELL STIMULATION IMPROVES STROKE RECOVERY**

Recent clinical trials of cell therapy have shown cell safety and some effectiveness in reducing after stroke disability. Cell therapy during the short period after stroke was related with stable clinical and imaging outcomes in the InveST and RECOVER studies, while the MASTERS studies shown good clinical effectiveness trends as same as to that observed in mouse models.

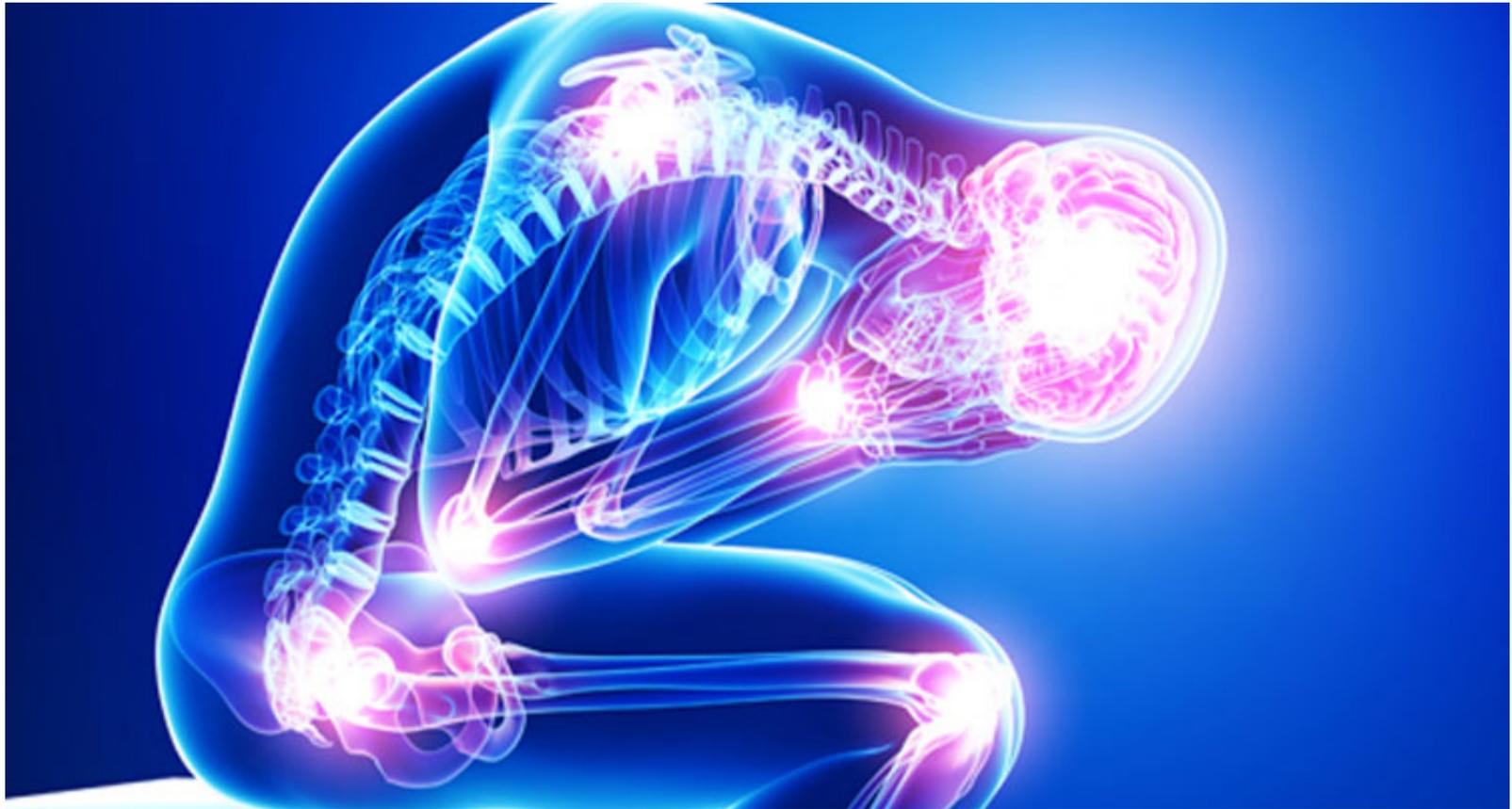
Cell therapy during the throughout stroke period was related with improved clinical outcomes in both the Sanbio and PISCES studies. The clinical studies reviewed used a variety of different cell types, delivery techniques and delivery locations each delivered with a variable delay from the time of initial stroke event. Even with these differences in trial design, there were no reported cell-related serious adverse event effects.

There are many proposed mechanisms by which cell therapy might help ameliorate recovery, which involve immune modulation, enhancement of blood vessel generation, nerve cells generation and production of growth factors and essential substances. Further exploration is needed to learn the specific effects of each type of cell therapy to develop the best combination of cell delivery technique, cell dosing, type of cells used, timing of transplantation, dead tissue area size and location of dead tissue that may benefit from further cell treatment for blood supply restriction type of stroke. (6)

## **STEM CELLS FOR SKIN REGENERATION FOLLOWING BURNS**

Stem cell treatment can improve the quality of burn wound healing, decrease the formation of scars and re-establish the normal function of the skin and its surrounding cells. The main origin of stem cells that may be used for repair and regeneration of damaged skin tissue are embryonic stem cells and adult stem cells.

Stem cells have ability of self-renewal and multipotency. Adult stem cells can produce skin cells. Mesenchymal stem cells can turn into multiple skin cell types and provide wound repair. Labeled MSCs can be observed in the epidermis, hair follicles, sebaceous glands, blood vessels and skin layer in full-thickness wounds. [7]



## **STEM CELLS TREATMENT FOR RHEUMATOID ARTHRITIS**

Stem cell treatment might help decrease inflammation and increase the residence of healthy cells in the body. The present-day knowledge on stem cell treatment as a possible treatment for Rheumatoid arthritis. Rheumatoid arthritis causes inflammation in the tissues between joints. This effects in a loss of cartilage, which is the connective tissue that cushions the joints. Over time, cartilage loss can damage the joint and surrounding bone. Mesenchymal stem cells (MSCs) are types of stem cell that be able to develop into bone and cartilage. Synovial MSC therapy means injecting these stem cells directly into the tissues surrounding the damaged joints. Some studies shows that Mesenchymal stem cells are also able to suppress the immune system and reduce the body's inflammatory reaction. This makes Mesenchymal stem cells treatment a promising treatment choice for autoimmune conditions such as Rheumatoid arthritis. [8]

## **HEARING LOSS**

Preclinical animal trials have shown that mesenchymal stem cells can be a promising new treatment for this problem. These findings have prompted experiments to start human clinical studies to assess the safety and effectiveness of mesenchymal stem cells for the treatment of sensory neuro hearing loss. The objective of the design systematic review is to examine the effectiveness of mesenchymal stem cells as a treatment for sensory neuro hearing loss in animal models. [10]

## **HEART DISEASE**

Regenerative therapies utilize stem cells for the regenerate of heart tissue have been widely used in preclinical and clinical trials during the past 16 years. Induction of new blood vessel synthesis to create a new collateral vessels within an area which lack of blood flow has been in evolution since the mid-1980s, soon after the first trial in human body reports on the blood vessel generation effect of recombinant fibroblast growth factor (FGF). There are multiple factors that significantly contribute the efficiency of stem cell treatment. Optimal delivery methods are essential for the precise delivery of stem cells to the damage area of the heart muscle, settlement and differentiation. Among the different techniques, direct injection of cells into heart tissue still calling the most clinical attention. (9)

## **RETINAL DISEASE**

Subretinal used of mesenchymal stem cells repaired degenerating retinas in retinal degeneration models in mouse. An experimental trial showed that mouse mesenchymal stem cells acquired from culture activate Müller cell (a type of cell in retina) differentiation and exerted a cell production effect by secreting growth factors. It was also reported in experimental studies that factors secreted from human mesenchymal stem cells prevent light-induced retinal injury. Studies have shown that mesenchymal stem cells can turn into different retinal cell types. Huang et al. reported that mesenchymal stem cells differentiated into retinal pigment -like cells with share morphological characteristic. (2)

## **PARKINSON DISEASE**

Stem cells have the ability for self-renewal throughout unlimited replication, as same as the capacity to differentiate into any cell type within body. The capacity to direct the fate of these cells to become a dopaminergic neuron(nerve cell produce dopamine which related to Parkinson's pathology) possible therefore offers an unlimited number of cells that can be utilize for nerve cells grafting. Stem cell-based therapies are emerging as the most promising method for the development of a applicable regenerative treatment that could be used in a hugh number of patients. (11)

## **DIABETIC**

The systemic review analysis revealed that the intravenous delivery of mesenchymal stem cells is a better treatment approach for type 1 diabetes than others route of stem cells treatment. The results of stem cell treatment for type 2 diabetic the average patient age with type two diabetic was 56years. Stem cell therapy was performed in 11 studies [363 patients with type 2 diabetes]. Stem cell treatment improved the insulin daily necessity

levels, as well as hemoglobin A1C, and had a positive effect on these other measurable factor. (12)

## **KIDNEY DISEASE**

Stem cell-based technology has been bringing as a potentially promising method treating kidney disease. The mechanism is the kidney protection potential of adult stem cell treatment in experimental models of acute and chronic kidney injury. From different mechanisms at the basis of stem cell-induced kidney repairing. Specifically, cell engraftment, merging into kidney structures, or stem cells producing essential substance for kidney cells . (13)



## **FACIAL SKIN ANTI-AGING**

Adipose-derived stem cell [ADSC] and mesenchymal stem cell [MSC] as future anti-aging instruments to some magnitude, have provided a promising and efficient options in fighting skin and facial skin aging. Moreover, bone marrow-derived mesenchymal stem cells have exhibited similar ability to repair and rejuvenate aged skin. [15]

## **OSTEOPOROSIS**

The utilizing of stem cells for tissue regeneration has raised significant hope in widely fields of medicine, including musculoskeletal disease. Stem cell treatment for osteoporosis can potentially decrease the chance of fractures and replace lost mineral density by either increasing the numbers or restoring the function of residual stem cells that can multiply and turn into bone-forming cells. Such osteoporosis treatment can be done by introduction of non-bone marrow origin mesenchymal stem cells (MSCs), typically obtained from bone marrow, umbilical cord blood tissue and fat. (14)

## **STEM CELL THERAPY ERECTILE DYSFUNCTION IN DIABETIC MEN**

The Mesenchymal stem cells is by far the most common used cell types in the field of urology and the most favorable method of stem cells delivery in erectile dysfunction therapy is injection stem cell into shaft of penis, given its ease of delivery and has proven effectiveness in both preclinical and clinical trials. The regenerative abilities of stem cells are likely achieved by production of various growth factors into the blood stream and/or migration of these factors to major pelvic nerve in addition to cell contact, essential substance signaling system and cellular transformation. The first reported clinical studies of stem cells treatment in diabetic men with erectile dysfunction showed a reasonable improve in penile hardness after a single injection of umbilical cord blood stem cells. While penile hardness was stabled for more than 6 months. In a different study on the use of stem cells in men with erectile dysfunction after prostate surgery, Yiou showed that injection of bone marrow mononuclear cells seems to be safe and effective treatment for the erectile dysfunction for a period of 6 months. However, the decline in erectile function over time suggests a need to assess for repeated injections. (16)

## Reference

- 1.National institute of Health. " Stem Cell Information "
  - 2.Erciyes University Faculty of Medicine, Department of Ophthalmology, Kayseri, Turkey  
"Stem Cell Treatment in Retinal Diseases: Recent Developments "Turk J Ophthalmol  
2018;48:33-38
  - 3.American for cures " what the difference kind of stem cells" [https://  
americansforcures.org/stem-cells/what-are-the-different-kinds-of-stem-cells/](https://americansforcures.org/stem-cells/what-are-the-different-kinds-of-stem-cells/)
  - 4.Prokhorova TA et al. Teratoma formation by human embryonic stem cells is site  
dependent and enhanced by the presence of Matrigel. Stem Cells Dev. 2009 Jan-Feb;  
18(1):47-54.
  - 5.Fabio Cofano "Mesenchymal Stem Cells for Spinal Cord Injury: Current Options,  
Limitations, and Future of Cell Therapy "International Journal of molecular medicine  
Published: 31 May 2019
  - 6.Cynthia L Kenmuir, Lawrence R Wechsler, Update on cell therapy for stroke. BMJ  
journal
  - 7.Wei Lu; Yong Jie Zhang; Yan Jin. Potential of Stem Cells for Skin Regeneration  
Following Burns, Expert Rev Dermatol. 2009;4(2):97-99. Medscape
  - 8.Medically reviewed by Brenda B. Spriggs, M.D., MPH, FACP on June 27, 2019 – Written  
by Charlotte Lillis, Stem cell therapy for rheumatoid arthritis, Medical News Today
  - 9.Radosław Litwinowicz, Bogusław Kapelak, Jerzy Sadowski, Anna Kędziora, Krzysztof Bartus,  
The use of stem cells in ischemic heart disease treatment, Department of Cardiovascular  
Surgery and Transplantology, Jagiellonian University Medical College, John Paul II  
Hospital, Krakow, Poland
  10. Kevin T. Chorath, Matthew J. Willis, Mesenchymal stem cells for sensorineural hearing  
loss: protocol for a systematic review of preclinical studies, BMC systematic review journal
  - 11.Thomas Benjamin Stoker. Chapter 9 Stem Cell Treatments for Parkinson's Disease,  
Department of Clinical Neurosciences, University of Cambridge, Forvie Site, Cambridge
  - 12.Fakher Rahim, Stem cell therapy for patients with diabetes: a systematic review and  
meta-analysis of metabolomics-based risks and benefits, Stem Cell Investig 2018;5:40
- 
- 1.Cinzia Rota, Marina Morigi and Barbara Imberti, Stem Cell Therapies in Kidney  
Diseases: Progress and Challenges, Int. J. Mol. Sci. 2019, 20, 2790
  - 2.Antebi B, Pelled G, Gazit D. Stem cell therapy for osteoporosis. Curr Osteoporos  
Rep. 2014 Mar;12(1):41-7.

3. Farshad Zarei, Abolfazl Abbaszadeh. Application of Cell Therapy for Anti-Aging Facial Skin, *Current Stem Cell Research & Therapy*, Volume 14 , Issue 3 , 2019

4. Eric Chung, Stem cell therapy in diabetic men with erectile dysfunction: a step closer to safe and effective regenerative technology, *Ann Transl Med* 2019

5. Da-Chuan Yeh, Tzu-Min Chan" Therapeutics of Stem Cell Treatment in Anti-Aging and Rejuvenation" *Stem Cell Discovery*, 8, 13-31.

6. Cheng-Liang Zhang, Ting Huang, Bi-Li Wu, Wen-Xi He, and Dong Liu" Stem cells in cancer therapy: opportunities and challenges" *Oncotarget*. 2017 Sep 26; 8

---

# **CHAPTER 4**

---

## **STEM CELL TREATMENT FOR ANTI-AGING**

---

# STEM CELL TREATMENT FOR ANTI-AGING

---

Aging is related with changes in dynamic social, environmental, physiological, behavioral, psychological, and biological processes. Some age-related changes are insignificant, for example graying hair. Others consequence in decline function of the senses and activities of daily life and multiplied susceptibility to and frequency of disease, disability or frailty. In fact, increasing age is the vital risk factor for a number of chronic and degenerative diseases in humans. (1)

## **AGING THEORY**

Nobody knows how and why people change as they get older. Some hypothesis claim that aging is trigger by injuries from ultraviolet light in a long period, wear and tear on the body, or side effect of metabolism. Other hypothesis view aging as a prearrange process controlled by gene.

No single theory can explain all the changes of aging. Aging is a complex process that diverg as to how it influences in each individual and even different organs tissue. Most scientists who study aging, feel that aging come from the interaction of many long-term influences. These influences include heredity, diet, environment, exercise, past illness, leisure, culture, and many other influencer.

Far from the changes of adolescence, which are expected to within a few years, each person ages at a difference rate. Some systems start aging as early as age 30. Other aging processes are not common up until much later in life. [2]

## ENVIRONMENTAL FACTOR ASSOCIATES WITH AGING

Examples of Age-related Changes in Function and Organ Structure and Possible Related Agents, Life-styles or Medical condition (5)

The environmental cause of aging by organ

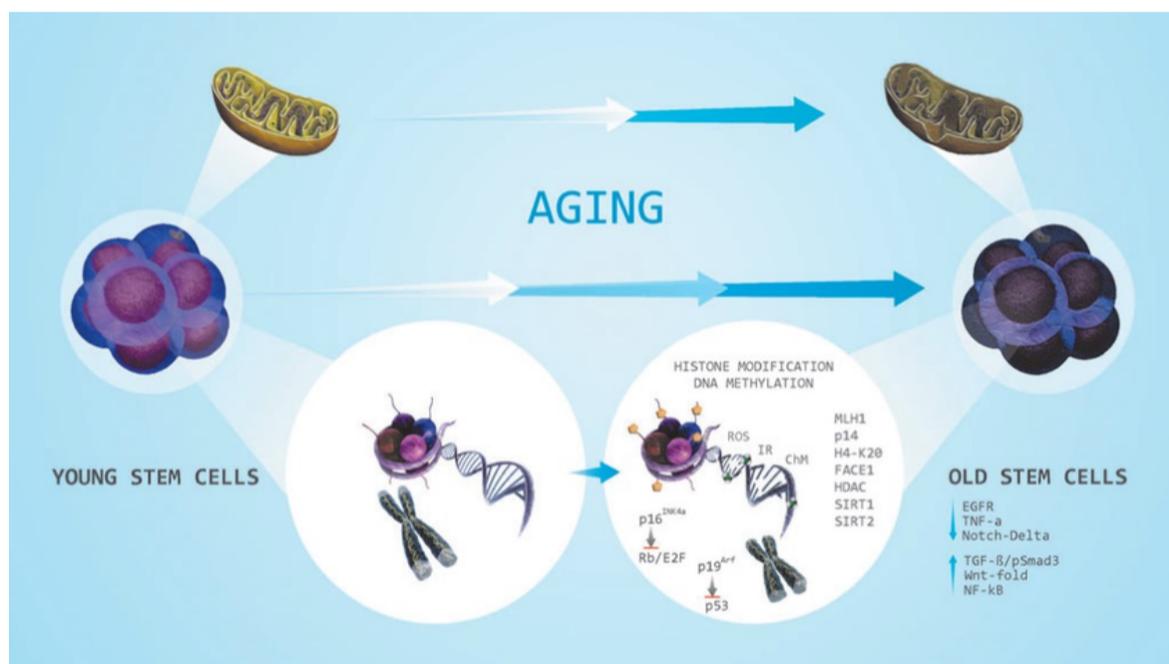
**Hearing loss:** loud noise, ears toxicity medication

**Nervous system:** Expose to toxin which effect nerve such as lead, mercury, food additive, pesticide

**Skin:** cigarette smoking, ultraviolet light, cigarette smoking

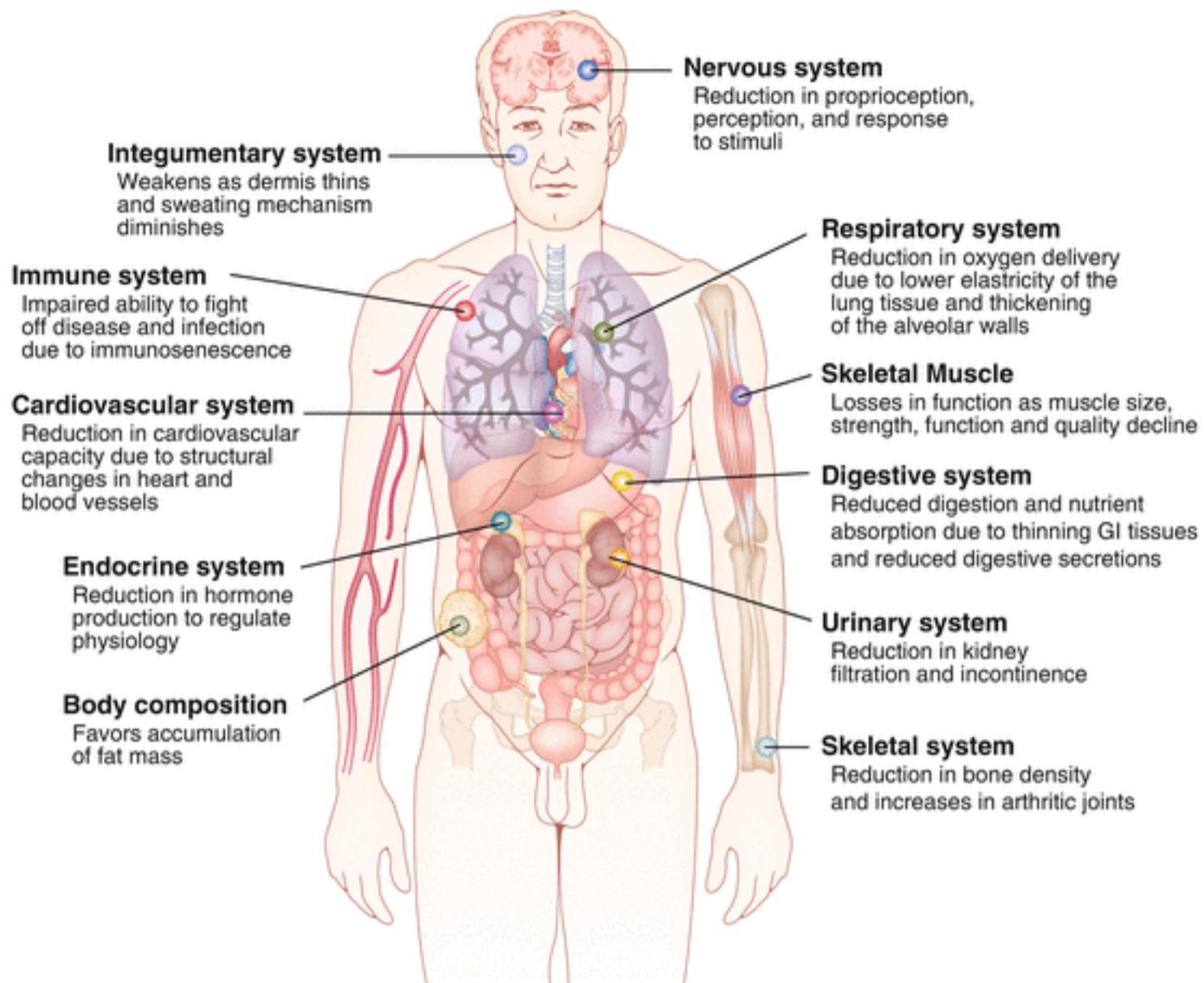
**Cataract:** ultraviolet light

**Respiratory system:** Cigarette smoking



## AGING MECHANISM

The fundamental mechanisms of aging the rate of buildup of stress-induced random molecular damage is conditional on the capacity of the antioxidant system and effectiveness of repair systems. As these systems are not 100% effective, cells always carry some unrepaired damage that conduct to activation of a stress response and increasing mechanisms to remove the damage or to prevent the cell break up. Though, these responses also become less effective with age so that damaged element buildup leading to cellular defects, which gives rise to tissue dysfunction and aging. (3)



## AGING CHANGE IN DIFFERENT ORGAN SYSTEM

Cells are the basic building blocks of tissues and organ. All cells facing changes with aging. They become bigger and are decrease their ability to divide and multiply. Among other changes, there is an intensify in pigments and fatty component inside the cell (lipids). Many cells lose their capability to function, or they start to function abnormally.

- **Skin:** freckle, skin tag, dry and sensitive skin, Hair loss  
Photoaging, skin laxity, wrinkle
- **Obesity:** easier to gain weight, the proportion of the body that is made up of fat increases on average from 14 percent to 30 percent between the ages of 25 and 75.
- **Sexual health:** menopause, erectile dysfunction, Dry Vagina, loss of sexual appetite
- **Endocrine system:** Diabetic mellitus type 2
- **Kidney:** Chronic kidney disease (4)
- **Respiratory system:** COPD
- **Cancer**

- **cardiovascular system:** High blood pressure, Ischemic heart disease, Valvular heart disease
- **bones, joints and muscles:** Bone shrink, Osteoporosis, Muscle loss, Osteoarthritis
- **digestive system:** Gall stone, Colon cancer, constipation, Indigestion,
- **Urinary tract:** Prostate gland Enlargement, CA prostate, Incontinence,
- **Brain and nervous system:** Depression, Parkinson, Stroke, Dementia, Alzheimer
- **Eyes and ears:** visual acuity defect, Macular degeneration, Cataract, Sensory hearing loss
- **Teeth:** increase chance of teeth and gum decay and infection

## **AGEING STEM CELL AND DEGENERATIVE DISEASE**

There is increasing proof that the aging process can have negative effects on stem cells. As stem cells age, their renewal capability decreases and their ability to differentiate into the various cell types is changed. Correspondingly, it is proposed that aging-induced deterioration of stem cell functions play a vital role in the pathophysiology of the varied aging-associated disorders.

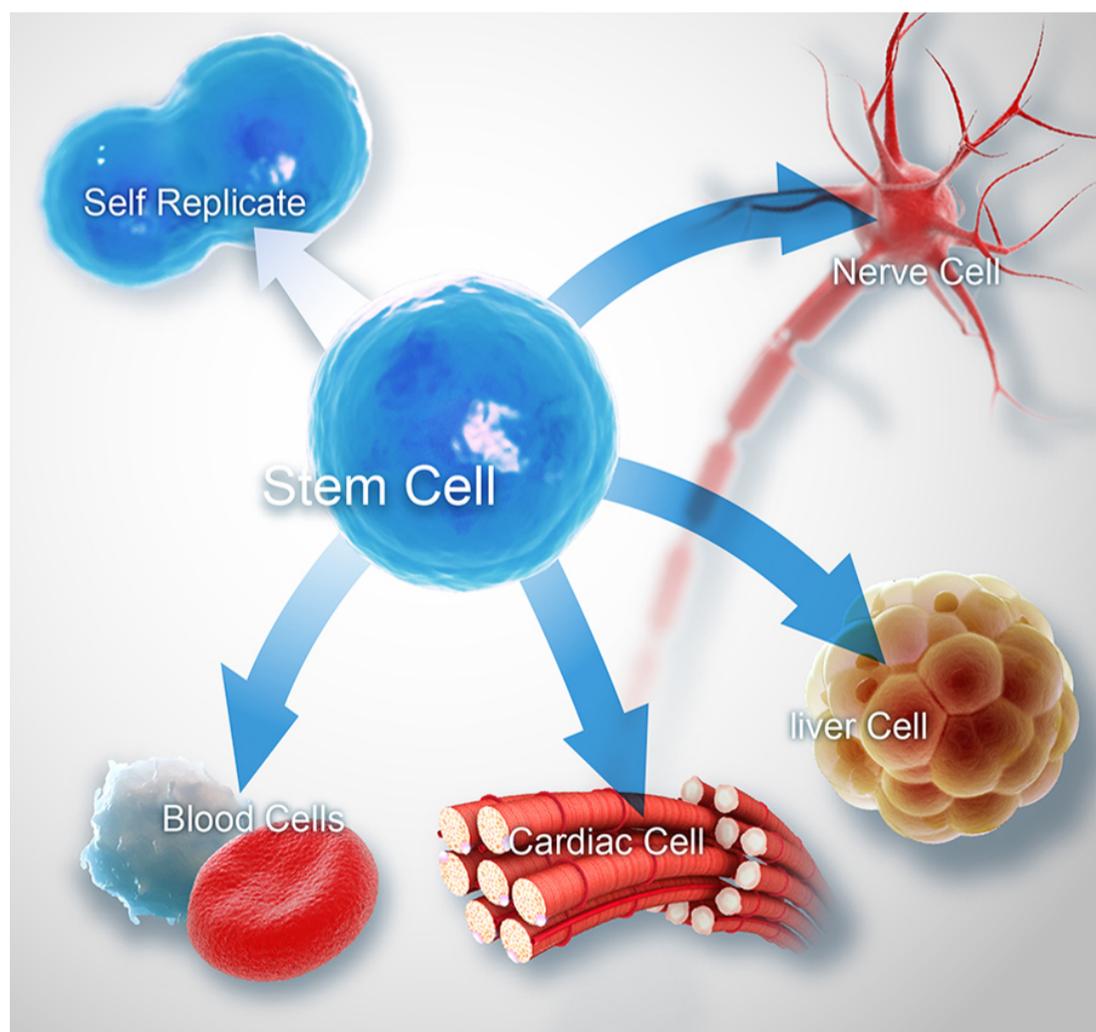
Adult stem cells, as known as somatic stem cells, are found through our body in every organs and tissue after development, and function as self-renewing cell pools to refill dying cells and repair damaged tissues through our life. However, adult stem cells seem to age with the person. As stem cells age, their functional capability also decreases. Specifically, this regenerative power seems to decline with age, as injuries in older individuals recover more slowly than in childhood. For instance, healing of a breaking bone takes much longer time in elderly than in young individuals. There is a considerable amount of proof showing that deterioration of adult stem cells in the adult can become a key role in the initiation of several diseases in aging.

From the various develop in stem cell research, it is transparent that we grow old partly as **our stem cells grow old with us**. The functions of aged stem cells become undermine as the result of intracellular cells pathways and surrounding environmental changes. With the sharp rise in the aging-related diseases, the need for efficient regenerative medicine method for the aged is more crucial than ever. (6)

## STEM CELLS FOR ANTI-AGING AND REJUVENATION

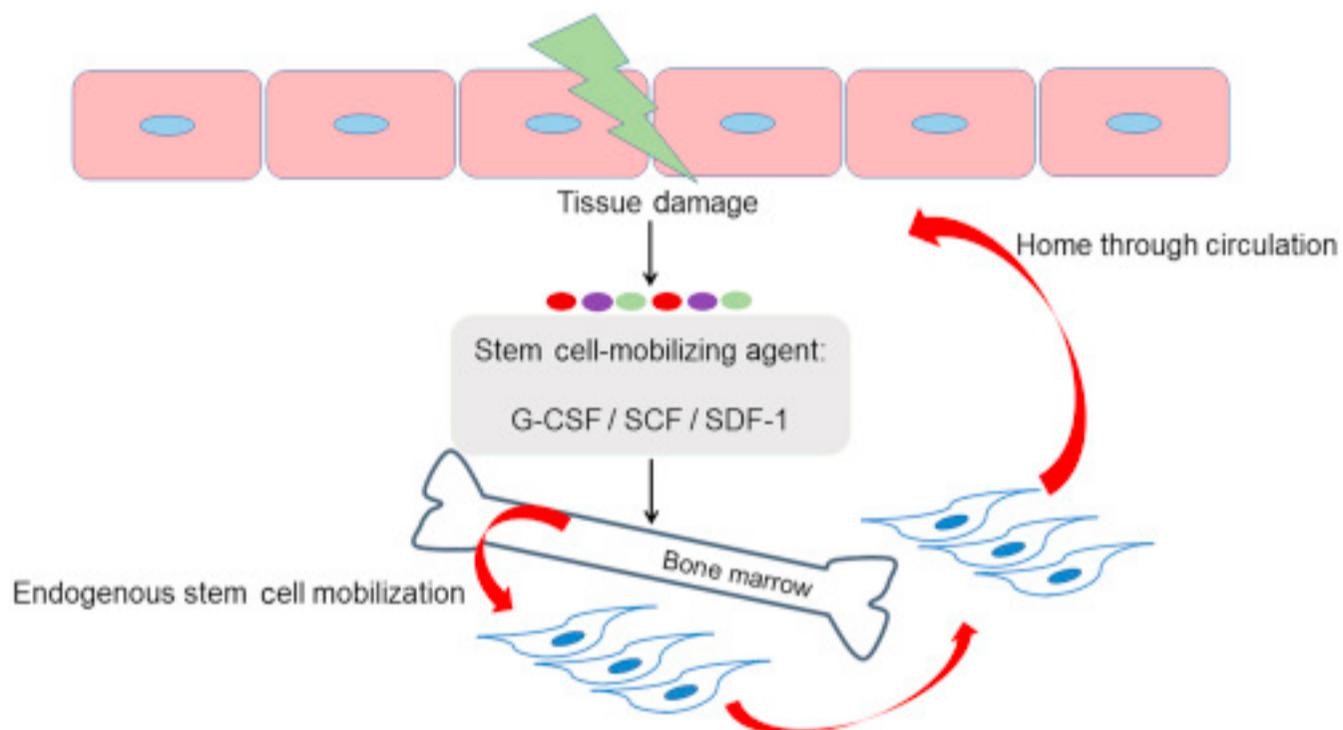
As stem cells age, their renewal capability decreases, and their potentiality to change into various cell types is exhausted. It is believed that stem cell failure causing a decline in health during aging process. Stem cell treatment is a potential method to induce and differentiate stem cells via cell replacement therapy allow an effective approach for the treatment of degenerative age-related diseases. It is believed that the regenerative ability of these cells is due to their high dividing ability and differentiation capabilities, essential substance production, and immune privilege.

Somatic stem cell resident varies according to the regenerative requires of the host tissue. In high turnover tissue, such as the hematopoietic or gut system, most stem cell or are active through our life. In organs deficient of stem cells, **stem cells transplantation to replace cells** is a potential therapeutic method for functional recovery. This means that stem cells can utilize for cell replacement therapy as a intervention target at reducing the effects of aging. (7)



## STEM CELL HOME COMING

Mesenchymal stem cells are another population of cells with treatment potential. Mesenchymal stem cells are normally defined as multipotent cells that has potential of self-renewal and can also generate a number of unique cell types that result in connective tissue, cartilage, and bone. Scientists have proof that these cells live in many parts of the body and are efficient of contributing to the repair of a various of damaged tissues and organs. Although injection or local transplantation prove therapeutically benefit, the potential to target these cells to particular tissues with highly effectiveness will be a key role in developing new therapeutic method.



**Inflamed or damaged tissues call for repairing by sending out signals**, some of which act as cues for mesenchymal stem cells and call them to the damage tissue, and many of these signals have been discovered, including stromal derived factor. Though stromal derived factor can be effective in calling mesenchymal stem cells, under normal conditions it stays in an inert state by enzymes in the body. (8)

After moving into injured tissues, mesenchymal stem cells will perform functions and aid wound healing of diseases and damage tissue.

## STEM CELL TRANSPLANTATION FOR ANTI-AGING, HOW DOES IT WORK?

Stem cells are identified by their multiple-efficacy and self-renewal abilities, resulting in the parent cells or mature cells that can repair tissue and keep the characteristics of stem cells to guarantee **long-term continuation** of the stem cell population. Stem cells play an important role in organ generation and maintaining homeostasis throughout life, own the **ability to migrate long distances and target disease or damaged conditions**, exhibit therapeutic genes, and respond to signal that redirect their differentiation into defective cell type. This means that stem cells can utilize for **cell replacement** as a treatment method aimed at decreasing the effects of aging. Stem cells mechanism of action such as:

- **Secrete essential substance:** Although there are many ways through which stem cells may decrease injury, the main mechanism which is assessed is through essential substance secretion functions.

- **Immune Regulatory:** In view of the inflammatory nature of most injuries, studies have shown that the important role of mesenchymal stem cells in resolving tissue damage counting on toning down inflammation in particular sites of injury.

- **Factor stimulating new blood vessel:** New blood vessel generate provided by mesenchymal stem cells can be appraise one more supportive effect, since the regenerate of blood supply is fundamental for repair of damaged tissues.

- **Anti-oxidative factors:** Some studies have proposed that mesenchymal stem cells also own anti-oxidative features. Mesenchymal stem cells have been observed to create many anti-oxidative substances such as superoxide dismutase (SOD), HGF, IGF, PDGF and IL-6. Mesenchymal stem cells respectively reduce oxidative damage in culture when fibroblast cells are exposed to oxidative damage-causing environments. (9)

- **Differentiation:** Mesenchymal Stem Cells have the ability to differentiate into multiple cell types such as bone, cartilage nerve cell, fat cell.

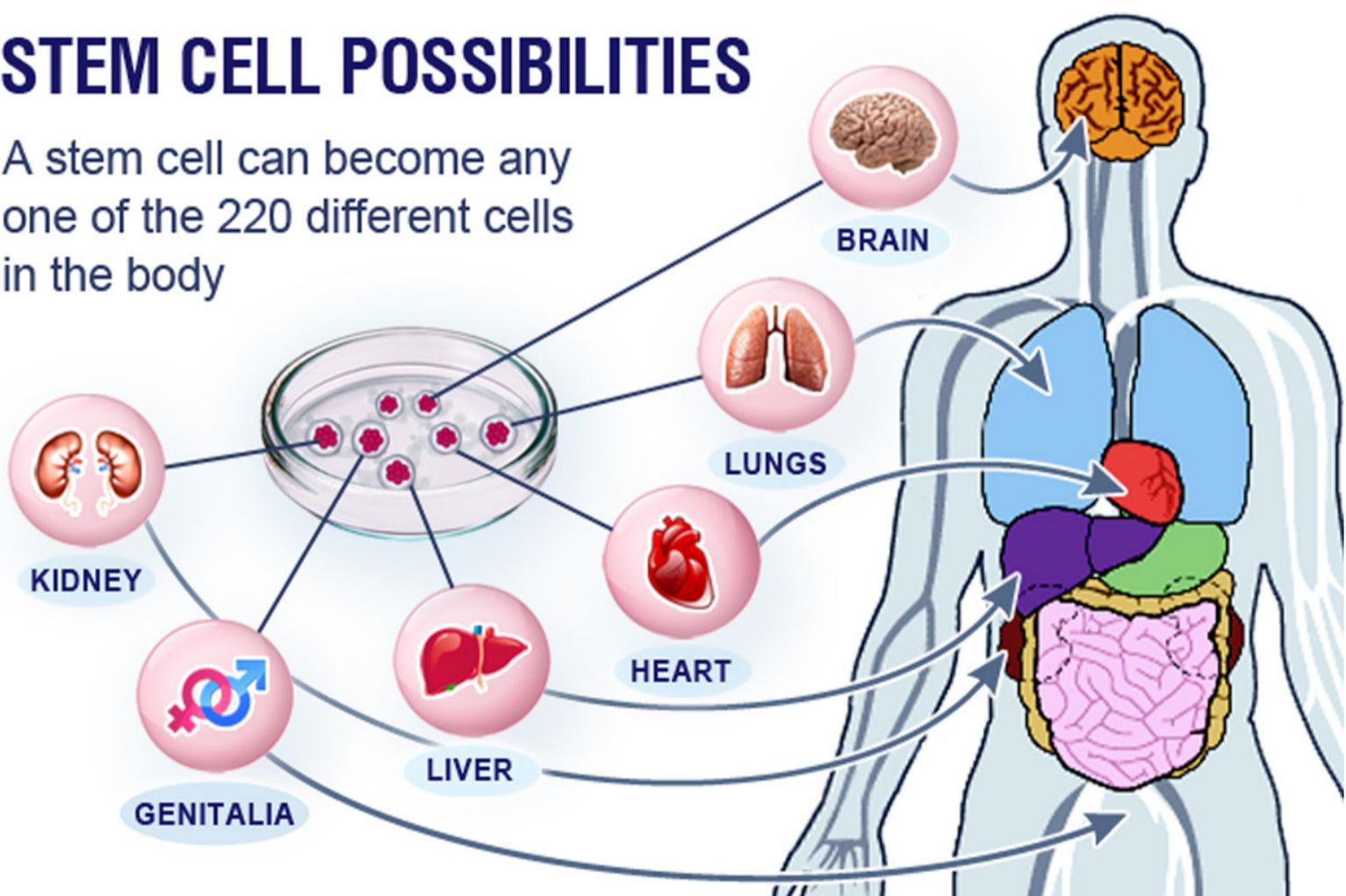
- **Fusion:** Specific adult stem cells can be used for clinical treatment by launching a nuclei or functional genes in aged or degenerating cells. Fusion of stem cells with degenerate cells play an important role in the regeneration of damaged tissue and organ. It's known that inflammation induce stem cells moving to sites of tissue injury. Moreover, inflammation also enhance the frequency of stem cell fusion.

## THE ULTIMATE REJUVENATION.

• **Immune System Rejuvenation:** This also applies to blood cell systems, in which aging is related with increased chance to blood cells cancer and other diseases. Blood cells are in charge of ongoing maintenance and immune protection of all cell types. Research on the process of blood cell genesis have shown that aging decreases immune responses and blood components, as a consequence an increase in the chance of white blood cells diseases, including cancer. Rejuvenation is intend to reverse aging more than simply delay it. Rejuvenation can be reach through the reconstitution of self-blood stem cells or the transplantation of hematopoietic stem cells, usually derived from peripheral blood, bone marrow, or umbilical cord blood.

## STEM CELL POSSIBILITIES

A stem cell can become any one of the 220 different cells in the body



• **Cardiac Rejuvenation:** Eventually, been recognized that heart muscle cells can be regenerated after birth. Patients with severe heart disease caused by the plaque builds up inside cardiac arteries, has decrease in the functionality of circulating stem cells to repair tissue damage. This has led a number of scientific researchers to use stem cell therapeutic as a means to regenerate of heart tissue as known as heart rejuvenation. Researchers have also examined cell therapies regarding the administration of healthy, young stem cells to a diseased heart to give protection from aging of cardiac cell and enhance cardiac repair.

• **Nerve System Rejuvenation:** Age-induced decrease in the number of nerve cells and neural stem cells compromise nerve cell regeneration. Aging of the central nervous system is related with the progressive loss of nervous system function, which can be aggravated by neurodegenerative diseases, such as dementia, stroke, Alzheimer's disease and Parkinson's disease. Most previous researches shown that cell therapy might be able to repair lost cells and enhance neuronal regeneration, protect nerve cell survival as well as play a key role in defeat permanent sensory loss or paralysis and restoring neurological function. The possible mechanisms may as the following:

- Inhibit cell death
- Secrete important substance
- Immune modulate function
- Promotion of nerve cell integration.
- Promote new blood vessel generation
- Generate nerve cell
- Decrease inflammation

• **Bone and Joint Rejuvenation:** Age-related changes in bone and joint include the destructive processes of cartilage. As the cartilage cells decreases, joint cartilage becomes increasingly thin, as well as dehydrate. It proves that the bioactive substance secreted by mesenchymal stem cells can have beneficial effects in modulating the microenvironment of damaged tissue, as a result better conditions for tissue regeneration. Mesenchymal stem cells produce a range of substance, which aid a variety of biological functions, including immune regulation, new blood vessel generate, anti-cell death, anti-oxidation, cell homing, and the promotion of cell differentiation. Mesenchymal stem cells have been used in cell therapy to enhance the repair of cartilage, bone, or muscle. Illuminating the mechanism that promotes the aging of bone and joint can lead to treatments target at slowing aging-associated changes or enhancing the regeneration of joint cartilage.[7]

## Reference

- 1.US Department of Human and Health Service, National institute on aging "Understand the dynamic of aging process "
- 2.US National library of medicine, Medline Plus "Ageing Change in organ tissue and cellar"
- 3.Mark T. Mc Auley, Modelling the molecular mechanisms of aging, Bioscience Reports (2017)
- 4.Mayo Clinic "Healthy aging " <https://www.mayoclinic.org/healthy-lifestyle/healthy-aging/in-depth/aging/art-20046070>
- 5.National Research Council (US) Committee on Chemical Toxicology and Aging. Washington (DC)" Environmental Effects on Age-Associated Diseases and Changes in Organ Function" National Academies Press (US); 1987.
- 6.Abu Shufian Ishtiaq Ahmed," Effect of aging on stem cells", World J Exp Med. 2017 Feb 20
- 7.Da-Chuan Yeh, Tzu-Min Chan" Therapeutics of Stem Cell Treatment in Anti-Aging and Rejuvenation"Stem Cell Discovery, 8, 13-31.
- 8.Harvard stem cell institute, Harvard University," Stem cells going home"
- 9.Patricia Semedo, Marina Burgos-Silva, "How do mesenchymal stem cells repair " open access peer review submit March 29 ,2011

---

# CHAPTER 5

---

## STEM CELL TREATMENT FOR KNEE OSTEOARTHRITIS

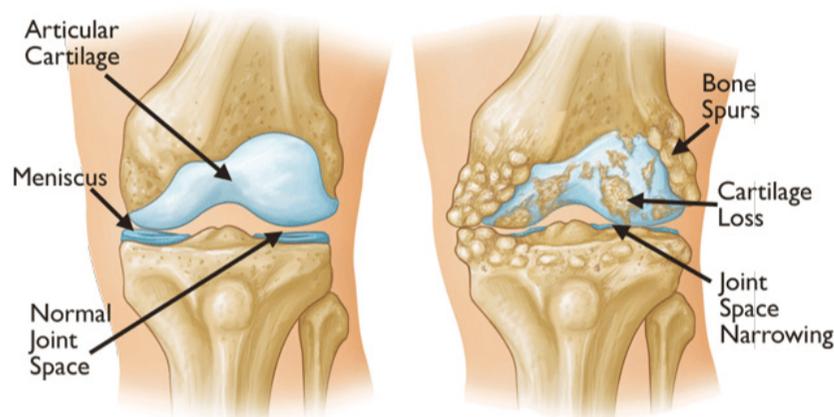
---

# STEM CELL THERAPY FOR OSTEOARTHRITIS OF KNEE

---

## WHAT IS OSTEOARTHRITIS?

Osteoarthritis is a condition which the cartilage (natural cushioning between joints) wears off. When this occurs, the bony part component of the joint rubbing more and more against each other as a consequence of decreasing cartilage, the shock-absorbing part. This rubbing creates in pain, stiffness, swelling, reduce ability to move and also sometimes the formation of bony projection along the bone edges. [1]



## SYMPTOMS

•**Loss of flexibility.** You may not be able to mobilize your joint throughout its full range of motion.

•**Grating sensation.** You may feel a grating sensation when you exert the joint, and you may hear crackling or popping.

•**Abnormal bone growth.** Bone spurs are the extra bits of bone, which perceive like hard mass, can form surround the affected joint.

•**Swelling.** This caused by the inflammation of soft tissue around the joint.

•**Pain.** Affected joints may painful after or during movement.

•**Stiffness.** Joint stiffness may be most detectable upon awakening or after being immobile for a long period.

•**Tenderness.** Your joint may feel painful when you press a light pressure to or near the joint.

## WHAT CAUSE OA KNEE?

Osteoarthritis has a multiple constituent etiology, which come from the influence of local and systemic factors. Osteoarthritis happens in all ages. The theory of this disease, in which particular responsible genes are related with its incident. Obesity, sports participation, genetic susceptibility and injury to the joint, predispose young athletes to the progress of premature osteoarthritis. History of knee trauma multiply the risk of knee osteoarthritis 3.86 times. Female gender, Old age, obesity and overweight, knee injury, bone density, repetitive use of joints, joint laxity and muscle weakness, all play roles in the development of joint osteoarthritis [3]

## RISK FACTORS OF KNEE OSTEOARTHRITIS

- Age
- Trauma
- Muscle weakness
- Joint laxity
- Mechanical forces
- Repetitive knee trauma
- Kneeling Squatting
- Meniscal injuries
- Genetic susceptibility
- Obesity
- Female gender

## OSTEOARTHRITIS KNEE, HOW TO PREVENT?

A number of risk factors might put a person at risk of developing osteoarthritis. Making changes may not reverse the condition, but a person may be able to decrease their risk or keep osteoarthritis from progressing.

•**Keep your healthful weight:** Excess weight puts more pressure on the knees. Over time, this give to wearing down the cartilage. Excess fat can also induce the body to secrete cytokines, a type of protein. This can lead to extensive inflammation, and it can turn the way that cartilage cells work.

•**Managing blood sugar:** High blood sugar levels can influence the structure and function of cartilage, and diabetes enhance the risk of cartilage loss and inflammation.

•**Regular exercise:** Moderate intense of exercise can keep the joints stay flexible, strengthen the muscles that hold up the knees, and decrease the risk of varieties health problems. It may help to walk, gardener, swim for 30 minutes at a time, five times per week.

Everybody who has not exercised for a long period, possibly due to hard work with mobility, should ask a medical professional for recommendation about how to start.

- **Reducing the injury risk:** Cartilage that has sustained damage from a repetitive injury is more prone to develop osteoarthritis later. It would be better to decrease the risk of slipping in the house by wearing shoes that fit well, and use protecting equipment while playing sports to save injury.

- **Keep away from overuse:** Some sports or professions related to repetitive movement of the knee joint, such as squatting or kneeling. People who usually lift more than 25kg might have an increased risk of osteoarthritis. Jobs that set people at risk such as unloading trucks or ships and laying carpets. Varying activities and getting adequate rest interval of work or exercise might help. [4]



## **OA KNEE TREATMENT OPTIONS.**

Osteoarthritis is a degenerative and progressive problem, with the damage structure is unlikely revert and repair. So, current treatment modalities are targeted towards symptom management until the degree of severity dictates the necessary of surgical treatment with joint replacement. [5]

- **Rehabilitation:** There are different treatment options for osteoarthritis, for example occupational, physical and alternative therapies.

- Physical therapy uses exercises to strengthen muscles and enhance flexibility and joint mobility.

- Occupational therapy target on helping you better cope your normal activities and lifestyle, for example get dressing, walking and bathing. You may only need these treatments for a short period as you learn to manage with your osteoarthritis or as your symptoms exacerbate.

○Alternative treatments for osteoarthritis can include massage, relaxation therapies and hydrotherapy. Acupuncture may also be useful. That acupuncture may be effective in decreasing osteoarthritis symptoms when used with additional medicines, or, in some scenario, in place of pain medication together.

○**Medication:** Many patients with osteoarthritis take medications to reduce pain and symptoms, such as:

○**Acetaminophen** This is frequently a first-line treatment for those with mild-to-moderate osteoarthritis pain. Common side effects such as upper stomach pain and nausea.

○**Nonsteroidal anti-inflammatory drugs (NSAIDs).** If acetaminophen can't provide relief, you may consider a Nonsteroidal anti-inflammatory drug for example ibuprofen or naproxen. These over the counter medicines can sometimes generate stomach problems. [7]

○**Supplement with hyaluronic acid:** Hyaluronic acid (HA), is a natural glycosaminoglycan produce by intra-articular cells which synthesis joint lubrication fluid. It provides viscous lubrication, has shocking absorbing features and additionally, possible anti-oxidant and anti-inflammatory functions have been reported. The current proof regarding effectiveness is conflicting

○Intra-articular injection treatment choices for knee osteoarthritis:



○**steroid injections:** steroid, can suppress immune response and interrupting the inflammatory cascade at multiple levels. It is believed that these are some of the process of increase joint mobility and pain relief in knee osteoarthritis. [6]

○**Intra-articular hyaluronic acid for knee:** Tend to be less beneficial than those for steroid injections. The 2013 American Academy of Orthopedic Surgeon guidelines strongly recommend against the use of hyaluronic acid for symptomatic knee.

# CELLULAR THERAPY FOR OSTEOARTHRITIS OF THE KNEE

---

## PLACENTA EXTRACT

Human placental extract has been used for decades in Japan and China as a treatment agent for liver endocrine abnormalities and regeneration. Placenta extract has been proof to have wound-healing, anti-inflammatory, and antioxidant effects in the clinical trial [6].

Placenta Extract enhance natural healing through nervous regulation, hormonal regulation, and immune- regulation, giving the body resistance toward disease. Placenta Extract carry variety of nutrients growth factor and anti-oxidant.

(You can see more detail placenta extract component follow this link <https://www.ivtherapybangkok.com/placenta-extract-bangkok>)

Osteoarthritis is an inflammation which rises because of degeneration (deformation) of the joints. When bones aging this cartilage can be punctured or wear out , and the pain of two bones directly rubbing against each other is the symptoms of osteoarthritis. The condition can go undetectable or if it isn't very severe, often with bouts of sudden pain.

Placenta extract can be used to successfully treat osteoarthritis. While placenta's Anti-inflammatory Function can work against the pain, its Tissue Repair ability promotes regenerate of the damaged tissues. Another feature of attack is its "Insulin-Like Growth Factor" which enhances growth of smooth muscle cells and cartilage and is remarkably efficient at treating and preventing osteoarthritis.

Professor Kazuhito Asano and his team at Showa University's Medicine Department described that high levels of active oxygen were observed in the joints of sufferers of osteoarthritis and rheumatoid arthritis, this is likely to be a cause of symptom degeneration and pain. Asano's group found active oxygen in the joints of 40 osteoarthritis patients and 19 rheumatoid arthritis patients who visited their university hospital and detected no active oxygen in the joints of healthy people. The severity of the symptoms of each patient were graded into four levels, and those with the most severe clinicals had on average 2.5 times in the case of osteoarthritis patients and five times the levels of active oxygen in the case of

rheumatoid arthritis patients and, compared to those with the least severe symptoms. They concluded that active oxygen was damaging the tissues in the joints and causing the condition to degenerate.

As placenta has an Active Oxygen eliminate Function it can play this additional beneficial role in rheumatoid arthritis and osteoarthritis treatment. [10]



## **STEM CELL THERAPY**

Stem cell treatment for knees is minimally invasive. It's a way that can decrease inflammation, repair and slow all these types of damage from joint inflammation, and prevent or delay knee replacement surgery.

In study, only one knee was injected. Although natural deterioration of the knee continues, at five years, those knees that are injected with stem cells are in better shape than they were before the injections.

## **STEM CELLS TREATMENT FOR KNEE MECHANISM OF ACTION**

Researchers believe that stem cell therapy for the knee works by:

- Developing into essential cartilage cells
  - Produce proteins called cytokines that slow degeneration of cartilage and reduce pain
- [8]
- Prevent the inflammation that can worsen arthritis

## **STEM CELLS THERAPY FOR KNEE, EFFECTIVITY.**

Recently, a group of researchers from the Krembil Research Institute, University Health Network in Toronto, Canada focused into the beneficial use of stem cells to treat knee osteoarthritis. They reported their results in the journal STEM CELLS Translational Medicine.

The researchers wanted to know whether it may be possible to regenerate and repair knee cartilage using mesenchymal stromal cells (MSCs). These cells can develop into a number of variety cell types, including bone, muscle, and importantly, cartilage.

In all, the researchers recruited 12 patients with moderate-to-severe knee osteoarthritis and extracted mesenchymal stem cells from each person's bone marrow. In this pilot study, one of the main aims was to understand what establish a safe and viable dosage, so the researchers injected each patient with one of three different doses of MSCs.

12 months after treatment, the researcher followed the patient, assessing their progress. For instance, they measured the inflammatory biomarkers level and the cartilage breakdown rate, and they check regular MRI scans of the affected joints. They also asked the participants to rate how well they felt they were doing.

By the end of the year-long study, the researcher found that there was a significant decrease in pain and an increase in quality of life.

There was a significant decrease in inflammation within the knee joints of the patients, which is crucial because experts now believe inflammation to be an important key driver of osteoarthritis. [9]

## **STEM CELL TREATMENT FOR KNEE SIDE EFFECTS**

Stem cell therapy for knees is noninvasive and infrequently painful. Side effects are minimal. The most common experiences after the procedure such as mild pain at the injection site, swelling. [8]

## Reference

- 1.WEBMD, Osteoarthritis, Reference "Osteoarthritis of the Knee (Degenerative Arthritis of the Knee)" <https://www.webmd.com/osteoarthritis/ostearthritis-of-the-knee-degenerative-arthritis-of-the-knee#1>
- 2.Mayo clinic , Osteoarthritis <https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925>
- 3.Behzad Heidari (MD), Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I
- 4.Medically reviewed by Gregory Minnis, DPT on August 15, 2018 – Written by Brian Wu, Medicalnewstoday.com "The stages of osteoarthritis of the knee"
- 5.Juan C Mora, Knee osteoarthritis: pathophysiology and current treatment modalities , Journal of Pain Research 2018:11 2189-2196
- 6.Keck School of Medicine of USC, Department of Orthopaedic Surgery, Los Angeles, CA, USA" Intra-articular treatment options for knee osteoarthritis", Nat Rev Rheumatol. Author manuscript; available in PMC 2019 August 01
- 7.Healthline, Medically reviewed by William A. Morrison, MD on January 3, 2017 – Written by Chaunie Brusie, RN, BSN, "Treatment for OA knee, what's work ? "
- 8.Medically reviewed by William Morrison, MD on August 21, 2018 – Written by Jennifer Leavitt, MS. "Can stem cell therapy repair the damage knee" Healthline
- 9.Written by Tim Newman on April 23, 2019 - Fact checked by Isabel Godfrey, MedicalNewsToday, " Using Stem Cells to combat osteoarthritis
- 10.Kentaro Yoshida, Placenta Power: For Health and Beauty A useful guide for those seeking placenta-based remedies

---

# **CHAPTER 6**

---

## **STEM CELL THERAPY FOR DIABETES MELLITUS**

---

# STEM CELL TREATMENT FOR DIABETIC MELLITUS

---

## DIABETIC MELLITUS, WHAT IS IT?

Diabetes mellitus (DM) is a metabolic disease caused by lack of insulin production or insulin dysfunction leading to high blood sugar as well as chronic metabolic change of protein, carbohydrate and fat. Chronic high blood sugar create many serious consequences, for example heart disease, kidney failure, and eye diseases. (6)

## DIABETIC MELLITUS COMPLICATION

Diabetes damage all parts of the body. It can cause severe, potentially life-threatening problems. For instance:

- **Atherosclerosis** – Atherosclerosis is fat accumulate in the blood vessel walls. This can compromise blood flow to every organs. The brain, heart and legs are most often affected.
- **Retinopathy** – Small blood vessels in the retina (the posterior part of the eye which sees light) can damaged by persistence high blood sugar. The damage can prevent blood flow to the retina and can cause bleeding into the posterior part of the eyes. In both ways will damage the ability of the retina to see light. Caught early, Retina damage can be limited by strictly control blood sugar level and using laser therapy direct to retina. Untreated retina damage can lead to blindness.
- **Neuropathy** – This means nerve damage. The most frequent type is peripheral neuropathy which mean the end organ nerve such as the nerve at hand and feet in trouble. The nerves to the legs are damaged first, giving pain and numbness in the feet. This can progress to cause abnormal pain and numbness in the legs and hands. Damage to the nerves that regulate sexual function, digestion and urination can also occur.
- **Foot problems** – Blisters and sores on the feet happen for two reasons:
  - o If peripheral nerve damage causes numbness, the person may not have sensation in the foot. The skin can break down, turn in to an ulcer, then the ulcer can get infected.

# Major Complications of Diabetes

## Microvascular

### Eye

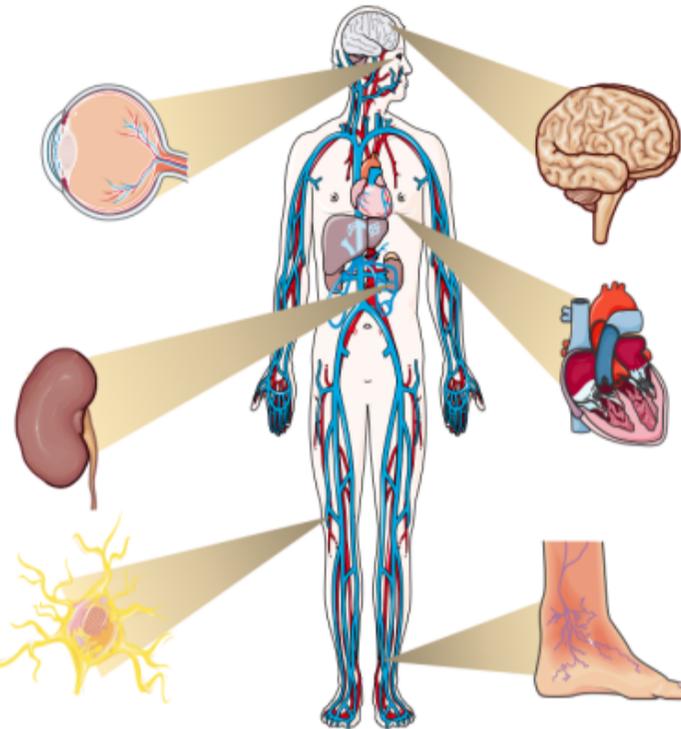
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

### Kidney

High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

### Neuropathy

Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



## Macrovascular

### Brain

Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

### Heart

High blood pressure and insulin resistance increase risk of coronary heart disease

### Extremities

Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

- o Blood circulation can be deficient, leading to slow progress healing. Left untreated, a small sore can become infected change into a large infective ulcer. If medical treatment can't heal the ulcer, an amputation may be required.
- o **Nephropathy** – As known as kidney damage. The risk is higher if blood sugars keep elevated and high blood pressure is not treated appropriately. (1)
- o **Eye damage.** Diabetes increases the risk of serious eye problems, such as glaucoma and cataracts, and may damage the retina blood vessel, potentially leading to blindness.
- o **Slow healing of the wound.** Left untreated, blisters and cuts can become severe infections, which may heal poorly. Serious damage might require foot, toe or leg amputation.
- o **Hearing impairment.** Hearing impairment are more frequent in people with diabetes.
- o **Skin conditions.** Diabetes may give you more susceptible to skin disease, including bacterial and fungal infections.
- o **Sleep apnea.** Obstructive sleep apnea is frequent in people with type 2 diabetes. Obesity may be the main factor to both diabetes and obstructive sleep apnea. Treating obstructive sleep apnea may decrease your blood pressure and make you feel more

energy after good rest, but it's not clear whether it helps manage blood sugar control or not.

- o **Alzheimer's disease.** Type 2 diabetes appear to increase the risk of Alzheimer's disease, even though the reason is unclear. The worse your blood sugar control, the greater the risk seems to be. (2)



## **DIABETIC MELLITUS, TREATMENT OPTIONS**

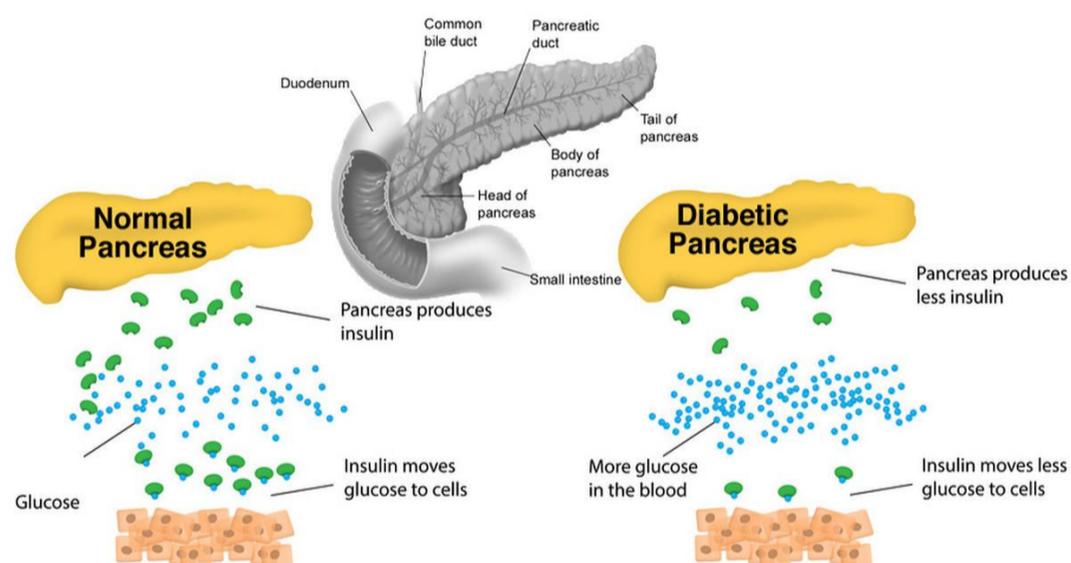
The key of diabetes management is regular exercise and proper diet , which have to be tailor made program. Both could be the only strategy needed for managing blood glucose in type 2 diabetes in its early phase. Patients with type 2 diabetes may need oral blood sugar decrease agents and/or insulin. The treatment strategy for diabetes may include

- exercise
- blood sugar lowering medications
- insulin
- management of complication and associated conditions and diabetic education
- nutritional recommendations and meal planning

The care of an patients with diabetes mellitus needs a multidisciplinary team. The key factor to success of this team are the patient's input, participation, and enthusiasm. Members of the health team include diabetologist, nutritionist and a diabetes educator. When the complications of diabetes mellitus appear, specialist such as podiatrists, neurologists, vascular surgeon, nephrologists, cardiologists and ophthalmologists are essential. Multidisciplinary diabetes care means that optimal diabetes management involves more than plasma glucose treatment. It should also detect and due with diabetes mellitus complications and modify DM -related risk factors. (4)

## TYPE 2 DIABETICS IS THE DISEASE OF AGING

Metabolic disorder including type 2 diabetes and heart diseases are closely related with the aging process. Truncal obesity and insulin resistance are the start of preconditions which related to metabolic disorder and heart diseases, commonly found among the elderly. Increase in body fat and decrease in lean body mass, especially internal organ fat accumulation that often come with aging, may related to the development of insulin resistance. As for the mechanism of type 2 diabetes, it is well known that aging causes a reduce of insulin sensitivity and change or insufficient compensation of pancreas cell functional mass in the face of rising insulin resistance. Related to pancreas cells functions, **aging associate with a reduce of pancreas cell regeneration capacity and increases sensitivity to program cell death.** It has recently been suggested that an age-related decline in mitochondrial function associate with insulin resistance in the elderly. Other metabolic disorder are also commonly related with aging such as coronary heart disease, cancer, vitamin D deficiency and cognitive disorders.



## HISTORY OF STEM CELL THERAPY RESEARCH FOR DIABETES

In 2011 (about 9 years ago), a pilot study in China about placenta origin mesenchymal stem cells to patients with chronic diabetes mellitus type 2 reported the stem cells transplantation was potentially efficacious, safe and easy. This study included 10 patients with chronic type 2 diabetes for more than 3 years, treating with insulin for at least one year, and poorly controlled blood sugar level. The patients received placental stem cells deliver by intravenous route. Six months after treatment, HbA1c and the insulin dosage measurements for all the patients shown a trend towards improvement. Furthermore, insulin release was also increase after mesenchymal treatment. Additionally, this study included a group of patients that translate closer to actual clinical scenarios, as they also had other co-underlying disease, such as kidney disease, heart disease, and vascular complications.

In 2013 Hu and his team conducted a single-center double blind study regarding the feasibility, safety, and preliminary outcomes of umbilical cord Wharton's jelly origin mesenchymal stem cells for new-diagnosis type I diabetics. The mesenchymal stem cell treated group had two intravenous infusions 4 weeks apart. Blood sugar level after meal and HbA1c assessment were lower in the experimental group between 9 months to 24 months after mesenchymal stem cells injection. Also, insulin utilize, and fasting C-peptide were remarkable improved in the mesenchymal stem cells group. The researcher report that in their study, the transplant of umbilical cord mesenchymal stem cells is practicable and safe.

In 2015, researcher from Sweden document the first trial aimed to evaluate efficacy and safety of autologous mesenchymal stem cells treatment in newly-case type 1 diabetics. Stem cells were originating from the pelvic bone marrow. They reported that administration of mesenchymal stem cells did not cause in adverse events in any of their patients.

Lately, scientist have created insulin-secreting mesenchymal and delivered them, in together with blood stem cells, to patients with type I diabetes. Autologous (stem cell from the themselves) transplantation injection direct to pancreas tended to have an improved C-peptide and blood sugar level after meal at 15-24 months when compared to allogenic(stem cells from other person) transplantation. Both researches viewed the stem cell administration as a safe treatment with potential benefit; however, larger studies will need to be performing to support their findings.



# STEM CELLS TREATMENT FOR DIABETIC MELLITUS

---

Recently, stem cell treatment has reached positive results in medicine regarding to the replacement, repair and regeneration properties. Of note, 3R therapy utilizes stem cells and as an effective implement to repair, prevent, replace and treat damaged organs. In fact, stem cell treatment has been used successfully in diabetes, from preclinical to clinical researches. (6) Stem cell transplantation is a great platform for diabetes treatment due to the fact that it can decrease the progression of diabetes and stop the complications of long-term blood glucose associated effect.

## **THE UMBILICAL CORD MSCS TREATING DIABETIC MELLITUS**

The most favored stem cell type that has been proven in diabetes mellitus therapy have been mesenchymal stem cells (MSCs). These cells have excellent potential and it is practicable to isolate them, there is an abundant source, and ethical problems are minimal.

Mesenchymal stem cells are distributed everywhere in the body and can then be extracted from multiple sources, for example the heart, bone marrow, skin, bodily fluids, and perinatal tissues. Mesenchymal stem cells respond to internal tissue environmental changes such as pH, oxygen, stress by producing immune modulatory factors known to regenerate injured cells and tissues. (5)

Studies have proven that mesenchymal stem cells can be extracted, expanded, and cryopreserved from both Wharton's jelly (umbilical cord matrix) and umbilical cord blood. However, advantages to the extraction of mesenchymal stem cells from the Wharton's jelly (WJ) include: a higher yield, increased likelihood of successful MSC isolation, more homogeneous stem cell population, and better potential to turn into insulin-producing cells. (5)



## **MESENCHYMAL STEM CELL TRANSPLANTATION FOR DIABETES MELLITUS**

It is known that MSCs play a crucial role in healing damaged tissues. They can differentiate to replace the dead cells as well as secrete stimulant factors to activate surrounding cells in the microenvironment, enhancing the tissue repair process. Therefore, MSCs can be applied to treat tissues impaired by chronic hyperglycemia. For T1DM, MSC transplantation can theoretically increase beta cell mass via the following effects:

- (1) beta cell replacement through in vitro or in vivo differentiation;
- (2) local microenvironment modification by production of cytokines, chemokines and factors to stimulate endogenous regeneration;
- (3) reduction or prevention of autoimmunity to beta cells. Although several MSC transplantation studies have clearly shown the outcome of controlled glucose metabolism, there have been observations of decreased insulin resistance as well as enhanced beta cell function effects. Moreover, the mechanisms of MSC treatment for T2DM still has not been well understood. Some studies have suggested that the immunomodulatory and inflammatory effects of MSCs are what contribute to the resulting reduction of insulin resistance. (6)

## **STEM CELL TRANSPLANT FOR DIABETES MECHANISM OF ACTION**

- **Cell replacement**

It has been proved that mesenchymal stem cells treatment can ameliorate blood glucose levels within the follow-up time from few weeks to several years. However, the

mechanism behind of this effect is still unclear. One mechanism is the replacement ability of transplanted mesenchymal stem cells derived cells. Mesenchymal stem cells are potentially to turn into insulin-producing cells and have been suggested to work instead of impaired pancreas cells in diabetic animals. Even though mesenchymal stem cells can be induced to produce insulin in in laboratory and in human body, few mesenchymal stem cells become fully functional pancreas in human body (only approximately 1.7 - 3% of transplanted cells). In addition, the temporary survival of transfused cells confirms that the replacement potential may not be the only reason of the therapeutic effect of mesenchymal stem cells. Sordi and team. have found the role of mesenchymal stem cells as support cells when they observed neovascular formation and normalized blood glucose levels after transplantation of pancreatic mesenchymal stem cells and islet mass.

- **Immune regulation:**

Not only the differentiation ability, mesenchymal stem cells have the special ability to regulate immune responses through multiple mechanisms. In laboratory, the ability to decrease immune system sensitivity of mesenchymal stem cells was discovered since the late 1990s. When stem cells culture with white blood cells, it is found that mesenchymal stem cells are able to change the cell division of multiple type of immune cells. They have potential to stop white blood cells generation and function. In particular, mesenchymal stem cells are able to modulate immune system to inhibit inflammation, resulting in reducing of insulin resistance in diabetes type 2. Mesenchymal stem cells are capable of reducing autoimmune responses in diabetes type 1.

It has been shown that mesenchymal stem cells can secrete many essential substance which modulate and improve the surrounding cells.

## **UMBILICAL CORD STEM CELLS, IMMUNE PRIVILEGE PROPERTY**

It has been proposed that mesenchymal stem cells are not only has ability to change into various kind of adult stem cells but also universal donor cells because their ability to avoid immune rejection. Furthermore, systemic delivery of mesenchymal stem cells derived from patient cells or other person source or even animal have been reported which can generate non-specific systemic immunosuppression. The transplanted mesenchymal stem cells could survive and differentiate in other person or animal recipients due to their immunotolerance capability. Atoui and team. have shown that the underlying mechanism of immunotolerance capability of mesenchymal stem cells come from their low immune triggering, immune modulation and immune suppression. As a result, transplanted mesenchymal stem cells can be tolerated (in part) in the recipients and

can produce local pancreatic stem cells to generate, leading to replacement of impaired cells in the diabetic.

## *Reference*

1. Harvard Health Publishing "Diabetic Type 2" Harvard Medical school
2. Mayo Clinic "Type 2 diabetic " <https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193>
3. International diabetes foundation "Type 2 diabetes"
4. EMRO Technical Publications Series 32" Guidelines for the prevention, management and care of diabetes mellitus" World Health Organization
5. Alvaro Moreira, Samuel Kahlenberg "Therapeutic Potential of Mesenchymal Stem Cells for Diabetes", J Mol Endocrinol. 2017 Oct
6. Loan Thi-Tung Dang ,Ngoc Kim Phan,Kiet Dinh Truong, "Mesenchymal stem cells for diabetes mellitus treatment: new advances " Biomedical Research and therapy

---

# CHAPTER 7

---

## STEM CELL TREATMENT FOR SKIN & HAIR REJUVENATION

---

# STEM CELLS TREATMENT FOR SKIN AND HAIR REJUVENATION

---

## **STEM CELLS TREATMENT IN AESTHETIC DERMATOLOGY (2)**

After many trial projects in the past 10 years of the 20<sup>th</sup> century, stem cells were around two decades ago introduced as a novel and promising treatment for many variety diseases. This expectation related with special characteristic of stem cells and their regenerative ability enhance in direct proportion to the important need in many medical fields.

Stem cells are right now extensively exploring for applications in a number of medical fields including skin. Mesenchymal stem cells seem to be a perfect source for tissue engineering therapy due to less of ethical concerns, high inaccessibility and increasing number of methods for extraction and expansion of such cell types.

Mesenchymal stem cells have anti-aging properties by decrease of melanin production after ultraviolet exposure as a result skin become whiter. An anti-aging effect of stem cells also may result from decrease cellular sugar metabolism, antioxidation and nutrient provider effect, which in result leads to restoration and rejuvenation of the functional capacity of the skin.

## **FACIAL AGING CHRONICLE**

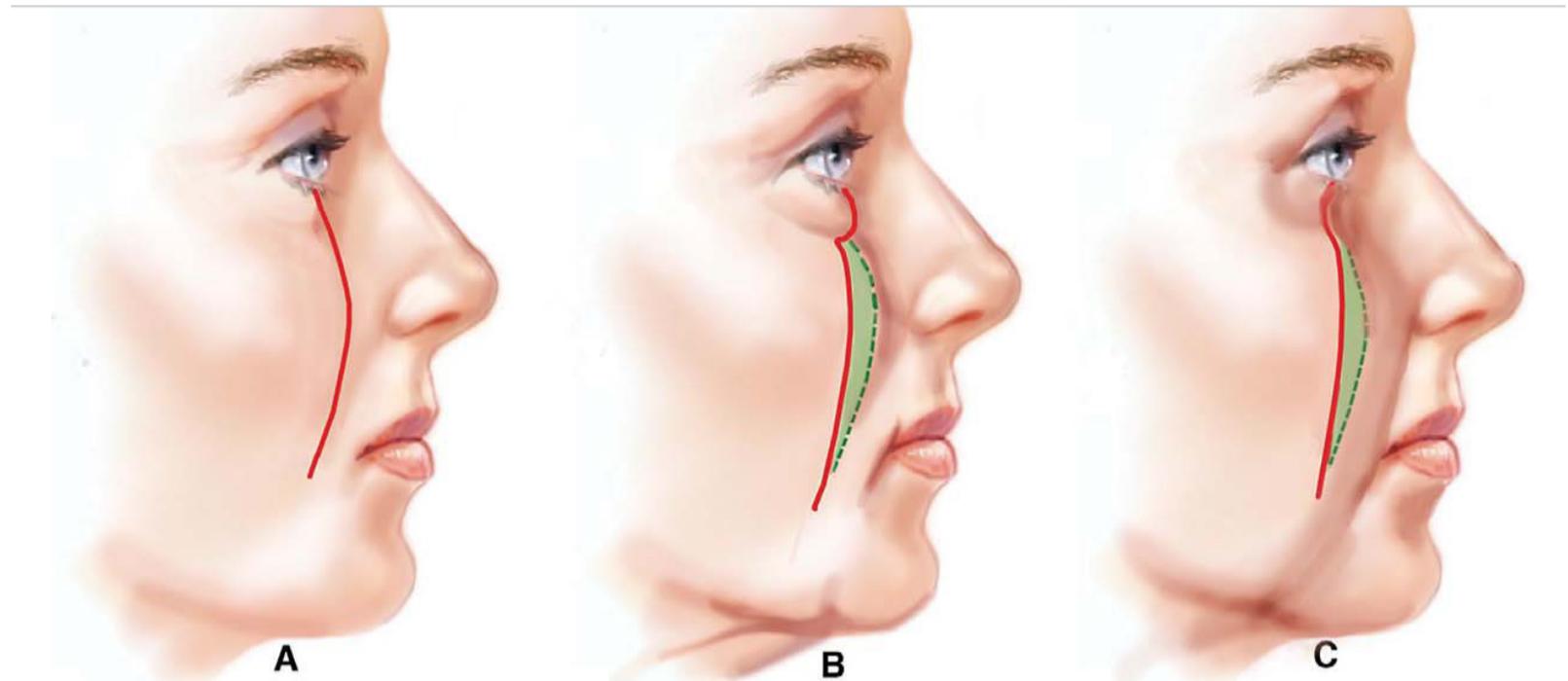
To rejuvenate a youthful facial feature, understanding of facial anatomical changes over time is essential. Anatomical changes to the facial skeletal framework, soft tissue, ligaments, fat compartments, and skin all impact to facial aging in different degrees depending on the intrinsic and extrinsic modifying factors. Here are the chronicle effects of aging toward our face. (1)

## **FACIAL SKELETON FRAMEWORK CHANGES FROM AGING**

Facial skeletal change with time, create dramatic shifting of the underneath soft tissue and supportive ligaments of the face, and when combined with baby fat redistribution and volume loss, these give a reasonable explanation behind the complex theory of facial aging. Changes to the bony structure with time lead to noticeable facial change and synchronize with soft-tissue laxity and atrophy, generate the appearance of facial aging.

## **FACIAL FAT AND SOFT TISSUE COMPARTMENT**

The collapse and loss of the facial fat compartments create the looks of enhance skin laxity or significant creases around the nasolabial area, around the eye's region, and jowl.



## **FACIAL SKIN AGING**

The skin is the cover or canvas of our face. The skin also aging as a result of internal and external factor too. Moreover, the repetitive dynamic muscle contractions from facial expression result in the presence of deep and shallow wrinkle over areas of contractions such as the around the eyes and around the mouth, forehead, and glabella. Photodamage and smoking increase production of oxidative stress toward skin cells resulting in thinning of skin thickness, sun damage skin, and collagen break, leading to aging skin characteristic.

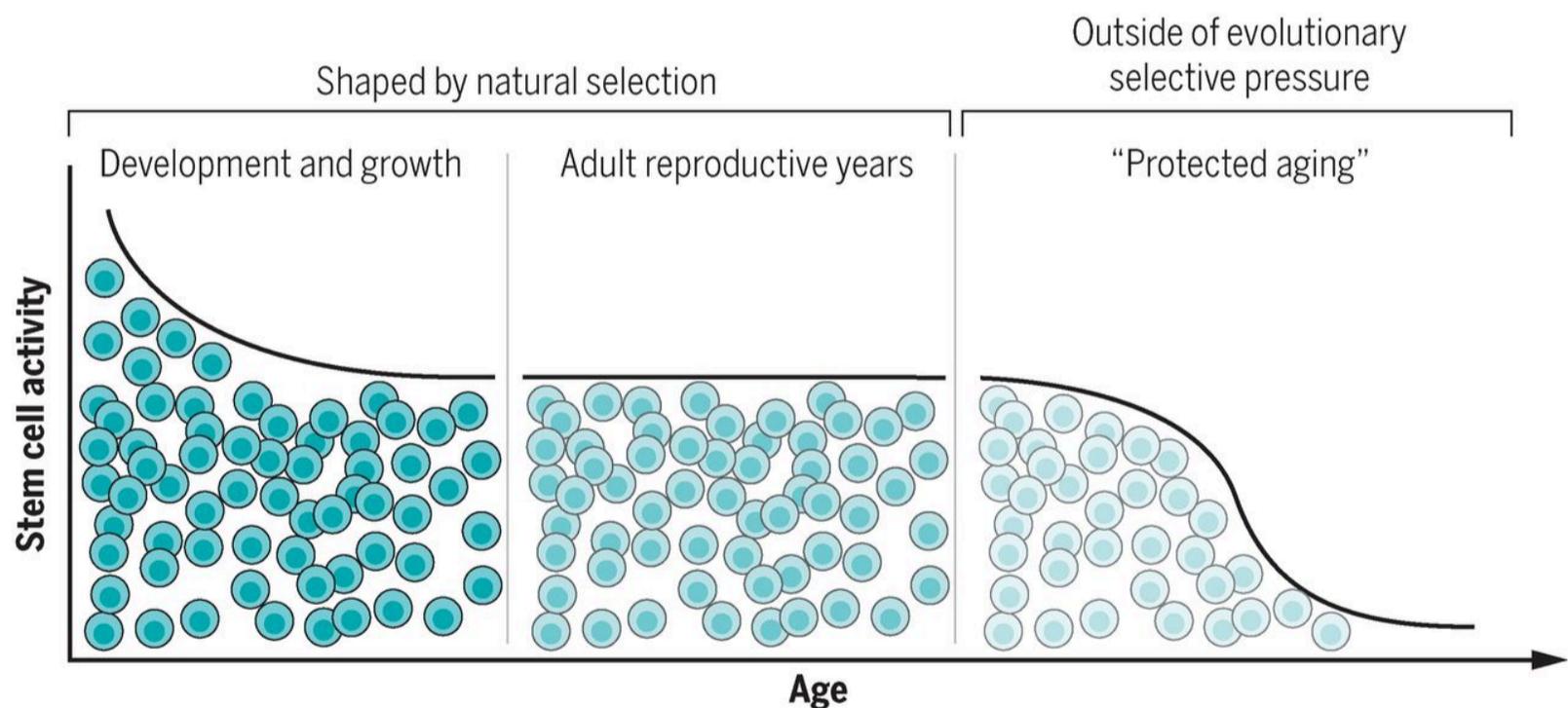
## **EXTERNAL FACTOR ASSOCIATES FACIAL AGING**

- Body mass index
- Hormones
- Alcohol consumption
- Cigarette smoking
- Unprotected sun exposure

## AGING STEM CELLS AGING FACE (3)

One major reason to Brough up stem cells into cosmetic treatment is the effect of age on the stem cells themselves. Stem cells are not immune to aging process, and their function is strictly regulated by their surrounding environment or called the stem cell niche. For example, studies have shown the blood stem cells have decreased functional potential with advanced age. Furthermore, aging is also related with reduced ability of the immune system and an increased chance of white blood cells diseases, including leukemias.

The functional reduce of aged stem cells come from a host of factors. Such as extrinsic factor, UV irradiation, genotoxic chemicals, and ionizing radiation and intrinsic factor such as oxidative stress, telomere shortening. With age, stem cells were found to DNA damage, and depending on the type and extent of this damage, the lesions in stem cells have the ability to drive cells to ageing, death, or tumor production. Therefore, as aging has been related with a cell-intrinsic reduce in the regenerative ability of stem cells, reported of rejuvenation in aged individuals by transfer of a young stem cells become more interesting.



## HOW CAN MESENCHYMAL STEM CELLS (MSC) MAKE YOU LOOK YOUNGER?

Mesenchymal stem cells are stem cells which have the unique ability to turn into various types of cells in the body. They are universal donor cells, which can be utilized into any patient without risk and are thus perfectly suited for Cell Therapy.

For aesthetic rejuvenation treatment, Mesenchymal Stem Cells can act as the start of building blocks for skin and connective Tissue, which include elastin and collagen, as well

for fatty tissue and blood vessel. They can turn back your skin age give you baby face looks, help the skin become more resilient, feel smoother, and appear brighter.

## **STEM CELL THERAPY FOR SKIN MECHANISM OF ACTIONS (4)**

Cell therapy is the injection of self or non-self stem cells to restore the viability of tissues. The mechanism of action of stem cell for skin such as

- Self-renewal: Stem cells have ability of self-renewal and turn into multiple type of cells which contribute to skin repair.
- Paracrine effect: Stem cells can enhance the progress of wound healing. By produce the substance that cell need for repair and regenerate such as variety types of growth factor and cytokine. These studies reported that the potential of stem cells to adjust the tissue microenvironment by production of soluble factors to tissue repair process.
- Immune system modulation: Stem cells can modulate the immune and inflammatory responses to enhance skin healing. The injection of mesenchymal stem cells on the surface of skin decreases inflammatory cell and increase the formation of new vessels tissue this make the underlying structure can reach more nutrient and substance needed for repair and regenerate. After skin tissue injury, Stem cells mobilize from blood. These cells migrate to the site of injury and modulate the repair and rejuvenate in the cellular level. It has also been identified that mesenchymal stem cells secrete cytokine which inhibit inflammatory and modulate immune response.

Taken together, it has been demonstrated that stem cells contribute to skin repair by several of their properties, including cell differentiation, substance secretion and immune modulation. Stem cell therapy is an attractive therapeutic tool for future skin treatment.

## **STEM CELL THERAPEUTIC EFFECTS**

- Blemishes and freckles become less visible as we can see that infant has none of all these skins aging sign
- Visible results start from 2-4 weeks and become outstanding within 2-3 months after stem cells therapy
- Repeat treatment recommended every 1-3 years
- Recovery time 1-3 days depend on skin type
- Slows and reverses visible signs of aging
- Revives skin cells, decrease fine lines and wrinkles
- Return of natural moisture to skin
- Return of resilience and firmness to skin

## **UMBILICAL CORD STEM CELLS THE BEST SOURCE OF MESENCHYMAL STEM CELLS**

Amniotic fluid stem cells (AFSCs) or umbilical cord blood stem cells (UB-MSCs) and Warton's jelly (WJ-MSCs) were also use in dermatological disorders. These cell types have greater cell division and variety cells transformation potential compared to mesenchymal stem cells from fat cells and Mesenchymal stem cells from bone marrow.



## **MESENCHYMAL STEM CELLS TREATMENT FOR SCAR**

Two million mesenchymal stem cells were injected directly into the scar from open chest surgery. A significant tissue regeneration and pain reduction was observed about 12 weeks after treatment start, cells were injected three times.

In another research, mesenchymal stem cells origin from fat cells were analyzed as a cell source for the full-thickness wound repair. Compared to control, the stem cell treatment group resulted in decrease of scar size and better color, quality and pliability of skin. Mesenchymal stem cells also used for treatment of face scars.

Self-extracted mesenchymal stem cells from fat cells in fibrin spray was used for therapeutic of acute and chronic poor healing wounds in 10 patients. In acute wounds, complete healing was reported 7-8 weeks after the treatment and within 16-20 weeks in participant with chronic wounds.

Mesenchymal stem cells were also utilized for preventing skin graft contraction after transplantation in a patient with hypertrophic scars. Stem cells were injected into the scar. After 2-year follow up, the resulted in contraction decrease.

## **WOUND TREATMENT BY INTRAVENOUS STEM CELLS**

After intra-venous administration, mesenchymal stem cells migrate to the wound site and start the wound repair, which was confirmed on a mice trial. The results showed that such a link is a high potential method for soft tissue regeneration and repair.

## **STEM CELLS TREATMENT FOR SCAR TREATMENT MECHANISM**

Generally, stem cells have been involved in the healing of wounds. A number of studies have shown the effectiveness of stem cells in promoting superior and faster wound healing. The application of stem cells in wounds enhance more effective upper most skin layer repairing. Amniotic fluid origin stem cells have also been utilized in wound healing. Wound closure, angiogenesis and upper most skin layer repairing were faster in skin treated with the stem cells in comparison to those treated with fibrin collagen gel only. Moreover, their effect is from released important factors and not by direct interaction. These stem cells also shown to increase vascular regenerate in the wounds along with the rate of skin cells repairing. Additional, stem cells have the effect of activin signaling on the homing of stem cells to wound sites.



## **MESENCHYMAL STEM CELLS TREATMENT FOR BURN SKIN**

Burn wound repairing related with a series of complex processes. Burn injuries, especially serious ones, are proving to have traumatize effects on the patients. Stem cells have been recently utilized in this field to enhance superior healing of the wounds. Not only have stem cells been shown to induce faster and better healing process of the burn wounds, but also, they have reduced the inflammation levels with decrease scar fibrosis and progression. (5)

Stem cells have a very promising capacity in the therapeutic of burn wounds; however, other therapeutic methods are being invented to improve the treatment. Stem cells are

commonly derived either from umbilical cord, bone marrow, skin, or v. Natesan and team have even used a part of burn wound itself as a source of stem cells for wound healing and regeneration. The dermal stem cells created in the study reduced wound contraction leading to a better skin cell repairing.

**Conclusion,** Stem cells enhance wound healing by a complex series of pathways that promote new blood vessel generate, collagen deposition and new tissue formation. They alter cellular immune response by reduce the severity of the inflammatory reaction. This may reduce the risk of infection. Stem cells are important in regeneration of cutaneous organ such as sweat, hair follicles and sebaceous glands, which would improve aesthetic outcomes for patients. (6)

## **MESENCHYMAL STEM CELLS TREATMENT FOR HAIR LOSS**

Wharton's jelly is a gel-like material which is present inside the umbilical cord. It has become a good resource of stem cells because it is widely available, it is noninvasive and painless for the extraction process no risk to the donor. There is also no ethical issue, has immune privilege potential, and can grow and multiple easily.

*Yoo and team* analyzed the effects of human mesenchymal stem cells on faster wound healing and the growth of hair follicles. Enriched mesenchymal stem cells were able to create new hair follicles. Growth factors may be added on during the culture process, which increase hair follicle growth.

Moreover, the effects of umbilical cord stem cells to hair pulp tissue growth were examined. Cells of the outer sheath of the hair were used for incubation and infused into the skin. Accordingly, hair follicle development was observed.

In 2015, Li and team. have reported a new type of stem cell from human umbilical cord blood which is cord blood-derived multipotent stem cell (CB-SC). Regarding to the team, clinical data have shown that a single therapy was able to create balanced immune responses that allowed the regeneration of hair cells. Immunohistochemistry shown the structure of a "ring of growth factor-beta 1" surround hair follicles, leading to the restoration of immune balance in the hair follicles and the protection of newly created hair follicles.

## Reference

- 1.Farkas, Jordan P. MD; Pessa, Joel E. MD; Hubbard, Bradley MD; Rohrich, Rod J. MD" The Science and Theory behind Facial Aging" Plastic and Reconstructive Surgery - Global Open: April 2013, Volume 1 Issue 1 page 8-15
- 2.Maciej Nowacki, Tomasz Kloskowski, Katarzyna Pietkun,Maciej Zegarski,Marta Pokrywczyńska," The use of stem cells in aesthetic dermatology and plastic surgery procedures. A compact review of experimental and clinical applications" Postepy Dermatol Alergol. 2017 Dec; 34(6): 526-534.
- 3.Adrian McArdle, M. B, B.Ch., Kshemendra Senarath-Yapa, M.B.B.Chir., Graham G. Walmsley, B.S.
- 4.Wei Lu; Yong Jie Zhang; Yan Jin" Potential of Stem Cells for Skin Regeneration Following Burns" Expert Rev Dermatol. 2009;4(2):97-99.
- 5.Fadi Ghieh, Rosalyn Jurjus,Amir Ibrahim, Alice Gerges Geagea,Hisham Daouk " The Use of Stem Cells in Burn Wound Healing: A Review" Review Article | Open Access Volume 2015 |Article ID 684084 | 9 pages
- 6.Eamon Francis, Laura Kearney, and James Clover " The effects of stem cells on burn wounds: a review" Int J Burns Trauma. 2019; 9(1): 1-12.

---

# **CHAPTER 8**

---

## **STEM CELL TREATMENT FOR INTERNAL ORGAN REJUVENATION**

---

# STEM CELLS TREATMENT FOR KIDNEY PROBLEMS

---

Remarkable progress has been made to advance stem cell therapy as potential treatment for kidney diseases: vary kinds of stem cells can rebuild renal function in preclinical trials of acute and chronic kidney injury. (1)



## **EXHAUSTED KIDNEY STEM CELLS, EXHAUSTED KIDNEY FUNCTION**

The influence of aging and of the underlying disease itself on donor stem cell ability is a significant constraint of autologous treatment but deserves discussion for donor stem cell transplantation for therapies. Donor cells are usually derived from healthy, young donors.

Mesenchymal stem cells from older kidney failure patients can be used to culture and inject back to the patient, but their therapeutic effects will be decrease with age and disease. The complex disease pathological is known to effects mesenchymal stem cells function such that mesenchymal stem cells from and stage kidney disease or diabetic patients are likely to be effective therapeutically compared to that of mesenchymal stem cells from healthy donors.

Several studies examined resident mesenchymal stromal cells (MSC) from kidney part of degenerate kidney. These kidney origin cells are not likely to be utilize for self-renewal as the population is exhausted over the course of progression of chronic kidney disease.

Mesenchymal stem cells of nonrenal origin such as adipose tissue, bone marrow, cord, placenta and blood are the most studied cells in acute kidney injury and chronic kidney disease. In acute kidney injury, either create by toxic substance such as chemotherapy, by severe systemic infection, or by shock state make kidney shortage of blood supply, mesenchymal stem cells have shown regenerative and protective effects. In chronic kidney disease, multiple evidence supports that mesenchymal stem cells treatment can decrease fibrosis and kidney dysfunction. mesenchymal stem cells limited chronic kidney disease progression and decrease glomerular pathology in kidney disease from diabetes. A meta-analysis in 2015 reported that injection of mesenchymal stem cells was most efficient cell type in slowing progression and development of chronic kidney disease. Increasing kidney function and improved kidney tissue fibrosis pathologies were the most changes observed after mesenchymal stem cells treatment. After kidney cells damage induced by chemotherapy mesenchymal stem cells can improve kidney cell function. In addition to decrease of renal structural abnormalities and reduce protein in urine, kidney inflammation can also be improved by mesenchymal stem cells.

# STEM CELL TREATMENT FOR LUNG PROBLEMS

---

Many lung problems still incurable and progressive to have significant morbidity and mortality. For example, emphysema, chronic obstructive pulmonary disease, or less common problems but such as cystic fibrosis, pulmonary fibrosis, pulmonary hypertension. Even though symptomatic care for these problems has improved, lung transplantation remains the single option for many patients. Additionally, lung transplantation is often a difficult choice since five-year mortality of approximately 50% and many problems related with the required lifelong immunosuppression.

Scientists believe that failure of respiratory system stem cell repairing function may be the cause of chronic lung diseases such as emphysema.



## **MESENCHYMAL STEM CELLS TRANSPLANT “THE REPAIRING EFFECTS”**

The repairing abilities of mesenchymal stem cells to the lung in chronic lung disease models was mainly created by multiple paracrine factors (the important substances which cells need for repair) produced by transplanted mesenchymal stem cells. These factors can decrease inflammation, induce immune modulation, enhance the permeability of gas exchange cells, and improve tissue repair. Even the few regenerated lung cells from exogenous mesenchymal stem cells also have contributed to functional restoration by replacing the damaged structures. (4)

## **STEM CELLS TREATMENT FOR COPD, THE PROTECTION AND REGENERATION**

Chronic Obstructive Pulmonary Disease is currently the fourth leading cause of death worldwide. Approximately 20% of patients with Chronic Obstructive Pulmonary Disease have emphysema, which means the destruction of alveolar walls, creating enlargement of air spaces. Patients usually die from progressive respiratory failure, and even with advances in treatment, there remains no cure.

Several studies have evaluated the role of stem cells on regenerating the lung in mouse emphysema models. These studies utilized transplantation of stem cells into

emphysematous mice and reported that there were reduced emphysematous structural changes. Another study systemically delivery stem cells immediately following irradiation to destroyed mouse lung. These data shown that stem cells can protect against progression of emphysema. The potential mechanism is seeming through paracrine effects (stem cells produce the important substance that cells need for rejuvenate) resulting in reduce alveolar cells death after injury.

## **STEM CELLS TREATMENT FOR ASTHMA**

The study, published in the foundation of American societies for experimental biology, reported that the mesenchymal stem cells can effectively decrease inflammation, reversed signs of airway remodeling and completely repair airway/lung fibrosis and airway hypersensitivity. These cells were special on their own as they were able to efficient reverse the scarring tissue that creates to lung dysfunction and difficulty in breathing. They concluded that this may provide a new stand-alone treatment or an additional treatment for groups of asthma patients. (3)

# **STEM CELL TREATMENT FOR LIVER PROBLEMS**

---

The past 20 years have shown an explosion of clinical and research application of stem cells, changing the field of regenerative medicine. Stem cell transplantation has already been used to treat patients with liver disease, cancer, and other types of chronic diseases. Actually, stem cell-based treatment is effective in variety diseases and create new insights into the therapy of liver disease.

A number of clinical trials have shown the effectivity profiles of stem cell transplantation in patients with liver disease, including liver failure, liver cirrhosis, mechanisms, and efficacy of stem cell treatment.

## **THERAPEUTIC EFFECTS, OF STEM CELLS HOW DOES IT WORK?**

From their ability for multiple rounds of self-renewal and ability to change into many different types of cells, stem cells play an important role in numerous biological phenomena including anti-inflammation, immune modulation, anti-cell death, new blood vessel genesis, promotion of tissue repair, and production of growth factors. Mesenchymal stem cells are the most common stem cell source for fundamental and clinical research given the lack of ethical constraints related their usage and availability



## **STEM CELL TREATMENT FOR LIVER REGENERATION**

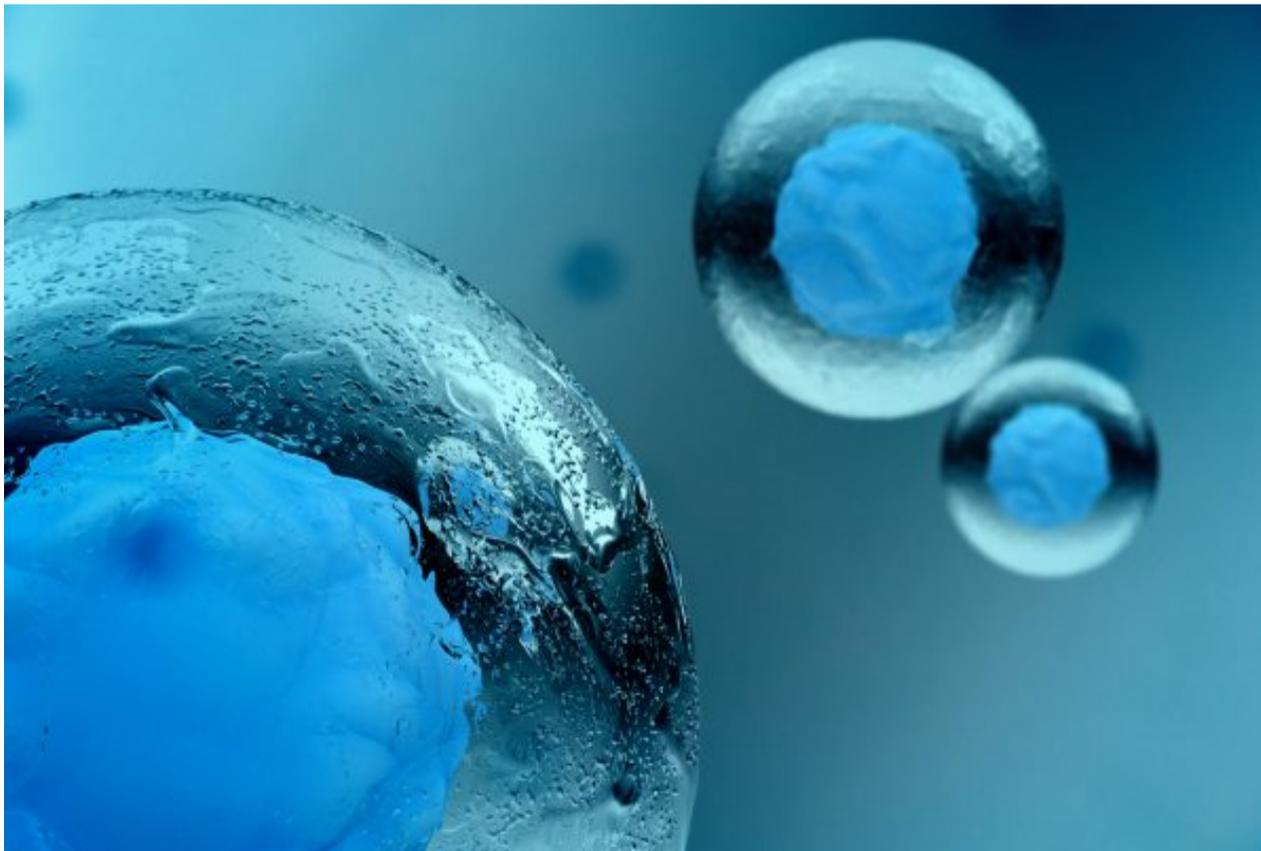
Until now, there have been numerous clinical trials on stem cell treatment liver disease, showing its side effects and efficiency features. Moreover, there were 139 clinical studies, including 27 ongoing clinical studies, on the association between liver disease and stem cell transplantation.

Prior trial indicated that mesenchymal stem cells transplantation can constitute an effective treatment for liver disease. In a multicenter, randomized, open-label, phase 2 trial, autologous mesenchymal stem, cells safely improved liver function and enhance the quantification of tissue adhesion following liver biopsy in participants with alcoholic cirrhosis.

Another open-label, paired, controlled study from China shown that injection of umbilical cord-derived mesenchymal stem cells also increased liver function and decrease fluid accumulation in abdomen from late state liver disease, in patients with chronic hepatitis B. Mesenchymal stem cells transplantation was also reported to increase liver function in chronic liver disease patients with autoimmune diseases.

Moreover, studies related animal models of acute liver failure have reported strong proof pointing to the success of mesenchymal stem cells transplantation in enhancing liver function, stop liver cell death, and increase liver cells production in animal models of acute liver failure, suggesting that mesenchymal stem cells transplantation may be benefits to treat liver failure. In 2012, Shi and team experiment a case-control study to measure the efficacy and safety of umbilical cord mesenchymal stem cells transplantation in chronic liver disease patients with acute-on-chronic liver failure; and found increased survival rates, together with decrease end-stage liver disease scores and improve liver function.

Another study on mesenchymal stem cells transplantation for the treatment of acute on top chronic liver failure patients also receive the same results, in which the treatment improves the 24 weeks survival rate, increase liver function, and reduce the chance of severe infections. Furthermore, a recent systematic review and meta-analysis of mesenchymal stem cells transplantation in acute on top chronic liver disease patients, which reported that the treatment remarkable decrease mortality rates, without increasing the incidence of severe complications. There were also no differences in the chance of severe complications such as brain edema, liver-kidney syndrome, gastrointestinal bleeding between the standard medical treatment and the mesenchymal stem cells treatment group.

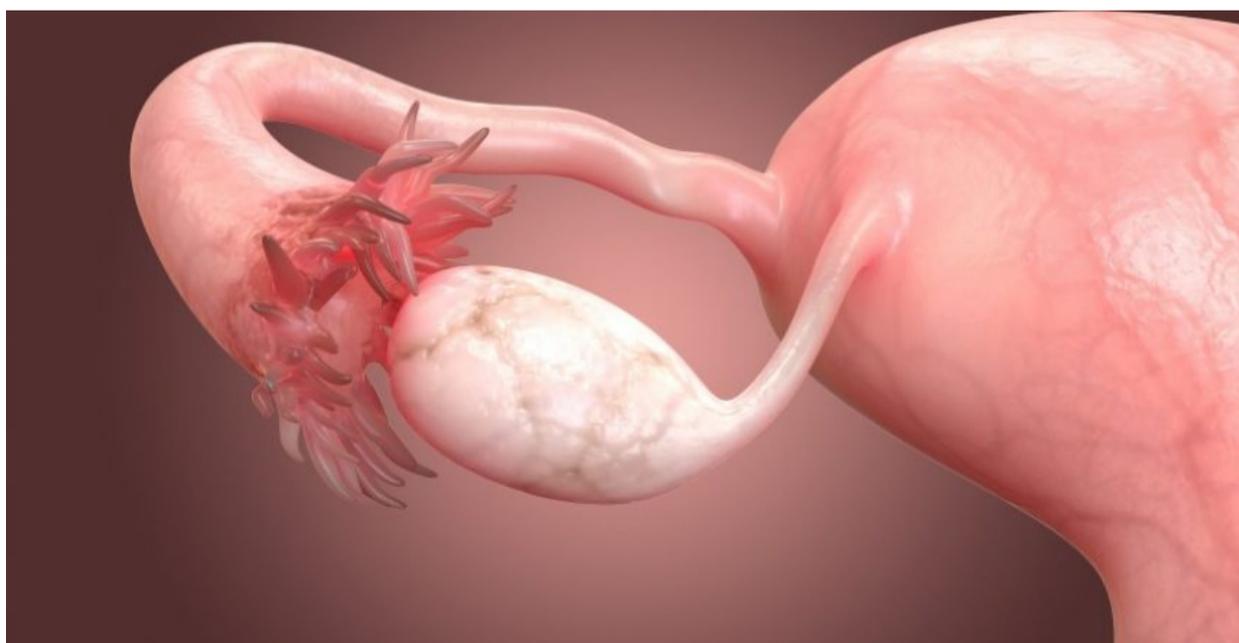


# STEM CELL TREATMENT FOR PREMATURE MENOPAUSE AND RESTORE FERTILITY

---

The data from a new trial name Rejuvenation of premature ovarian failure with stem cells (Rose) report that, in the two patient who have completed the treatment with stem cells transplantation to date, serum estrogen levels have increased as soon as 3 months after the injection, and the rejuvenate effect has lasted for at least one year. Their menopausal symptoms have been decreased, and six months after the injection of the mesenchymal stem cells. Ultrasound imaging of treated patient shows significant size enhance in the treated ovaries compared to the untreated one. So far, the patients have well tolerated with treatment, no side effects.

The ovaries produce hormones and eggs typically until menopause in the early fifties, when they stop working. About 1 percent of women have primary ovary insufficiency, and some are as young as in their teenage. With primary ovary insufficiency (the condition that ovary stop produce hormone without reasons), the ovaries stop working and the women start menopause. They lose the ability to ovulate and menstruate and they may be at enhanced risk for menopausal symptoms including night sweets, hot flushes, vaginal dryness and mood swings, and for osteoporosis-related fracture, cardiovascular disease and earlier cognitive function decline. (6)



# STEM CELLS TREATMENT FOR MEN HEALTH

---

A novel clinical study results show that stem cells can restore sufficient erectile function to allow impotent men to have sexual intercourse. In recent years a number of groups have worked to develop stem cell treatment as a therapy for erectile dysfunction problems, Results reported at the European Association of Urology conference in London manifest that 8 out of 21 have successfully return sexual function without the use of other medicines, injections, or implants. None of the 21 men reported significant adverse effects over the study period, or in the following year. After isolating the stem cells, they were injected into the muscular of penis. No overnight stay in hospital required. Within 6 months of the treatment, 8 out of the 21 patients shown that they had regain sufficient erectile function to achieve sexual activity.

This improvement has been stayed for a year, indicating that this therapeutic method may has long-term potential. Using the generally-accepted questionnaire to estimate erectile function, the whole group of 21 patients shown that their score had improve from 6 before the stem cell transplantation surgery, to 12 after 6 months. (7)

## **STEM CELLS TREATMENT FOR ERECTILE DYSFUNCTION IN DIABETES PATIENT**

Erectile dysfunction is common in diabetic patient from multifactorial such as neurological, vascular and hormonal change. The first reported clinical study of stem cells treatment in diabetic men with erectile dysfunction showed a reasonable increase in penile rigidity after intra-penile muscle injection of umbilical cord blood stem cells. While penile rigidity was stayed for more than 6 months. In a other trial on the use of stem cells in men with erectile dysfunction following prostate surgery, showed that intra-penile injection of mesenchymal stem cells appeared to be safe and improved the erectile function for a period of 6 months.

## *Reference:*

1. Julia Marcheque ,Benedetta Bussolati ,Marie Csete Laura Perin,“ Concise Reviews: Stem Cells and Kidney Regeneration: An Update “Stem cells translational medicine Received May 24, 2018
2. Viranuj Sueblinvong, MD1 and Daniel J. Weiss, M.D., PhD” Stem Cells and Cell Therapy Approaches in Lung Biology and Diseases” Transl Res. 2010 September; 156(3): 188-205
3. Monash University” Unique stem cells as a potential asthma treatment “June 28, 2017
4. Zhongwei Sun, Feng Li, Xin Zhou, Kian Fan Chung, Wen Wang” Stem cell therapies for chronic obstructive pulmonary disease: current status of pre-clinical studies and clinical trials” J Thorac Dis. 2018 Feb; 10(2): 1084-1098.
5. Dong-Bo Wu, En-Qiang Chen, and Hong Tang “Stem cell transplantation for the treatment of end-stage liver disease” World J Hepatol. 2018 Dec 27; 10(12): 907-910.
6. EndocrineSociety.org “Stem cell therapy may help reverse effects of premature menopause, restore fertility” Chicago, IL March 18, 2018
7. European Association of Urology - press release” Stem cells shown to restore erection capability in men with erectile dysfunction “

**REVIVAL CLINIC**

---

**BANGKOK**

---

**[REVIVALCLINICBANGKOK@GMAIL.COM](mailto:REVIVALCLINICBANGKOK@GMAIL.COM)**