Chapter 1

Discovery of Stem Cells

Ariyani Noviantari

A. Introduction

Stem cells have been attracting a lot of attention in recent years, and the application of stem cells has been recognized as an extremely promising and advanced research area being studied. Stem cells are a special kind of cell that can self-renew and specialize into distinct cell lineages. They are found in any stage of life. Because of their unique capacity for self-replication and differentiation, they are becoming a common form for the investigation of fundamental biological issues, including transcription, cell fate decisions, replication, division, and replication. Fundamental queries at various developmental stages can be answered with the help of adult stem cells, which can give rise to the cells within a certain lineage, and embryonic stem cells (ESCs),

A. Noviantari

National Research and Innovantion Agency, e-mail: ariy007@brin.go.id

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which can generate any cell type in the mammalian body (Poliwoda et al., 2022; Zakrzewski et al., 2019).

Stem cell research is developing exponentially, altering the character of medical care as it will be performed in the future. Innovation in the treatment of degenerative diseases is made possible by cell-based therapy and its products in regenerative medicine by promoting regeneration (Cho et al., 2018). Due to the presence of trophic factors secreted by these cells, stem cell products such as secretomes provide another potential alternative to stem cells (Kim et al., 2013).

Stem cells are distinguished by their ability to self-renew and differentiate into various types of cells like osteoblasts, chondrocytes, adipocytes, neurons, glial cells, cardiomyocytes, muscle cells, hepatocytes, endothelial cells, and other types of cells (El Barky et al., 2017; Laverdet et al., 2014; Macrin et al., 2017). Based on their ability to differentiate, stem cells are categorized into two groups: (1) pluripotent stem cells (PSCs), such as ESCs and induced pluripotent stem cells [(iPSCs) and (2) multipotent stem cells or adult stem cells (ASCs), PSCs, including ESCs formed from embryos and iPSCs derived by gene transfer, can proliferate indefinitely and differentiate into several types of tissues depending on their treatment conditions. However, multipotent stem cells, like mesenchymal stem cells (MSCs), can only differentiate according to their lineage and can be formed from mature tissues such as bone marrow, adipose tissue, umbilical cord blood, placenta, or blood. Additionally, ESCs and ASCs offer a great tool for cell therapy, which increases the importance of stem cell research in regenerative medicine (Chang et al., 2019; Zakrzewski et al., 2019).

Stem cells have a high potential to become one of the most essential parts of medicine. Furthermore, they contribute significantly to the advancement of regenerative medicine (Zakrzewski et al., 2019). However, there are still many gaps in our understanding of stem cells and their applications in clinical settings. This book had the objective to provide information on stem cells and their applications, starting with the chapter about the MSCs culture technique and continuing

with applying stem cells and their secretome in diabetic, neurological, orthopaedic, and cardiovascular diseases, and stem cells for anti-aging. Therefore, the book concluded with an ethically responsible approach to stem cell research.

B. The Understanding of Stem Cells

Stem cells are special cells with the capacity to differentiate into different kinds of cells or other tissues as well as the ability to regenerate themselves over an extended time (El Barky et al., 2017; Laverdet et al., 2014). Stem cells can develop into different types of cells and eventually become specialized (Zakrzewski et al., 2019). Although stem cells are undifferentiated, they can differentiate into a variety of cells, including osteoblasts, chondrocytes, adipose tissue, neurons, glial cells, cardiomyocytes, muscle cells, hepatocytes, endothelial cells, and others (Catacchio et al., 2013).

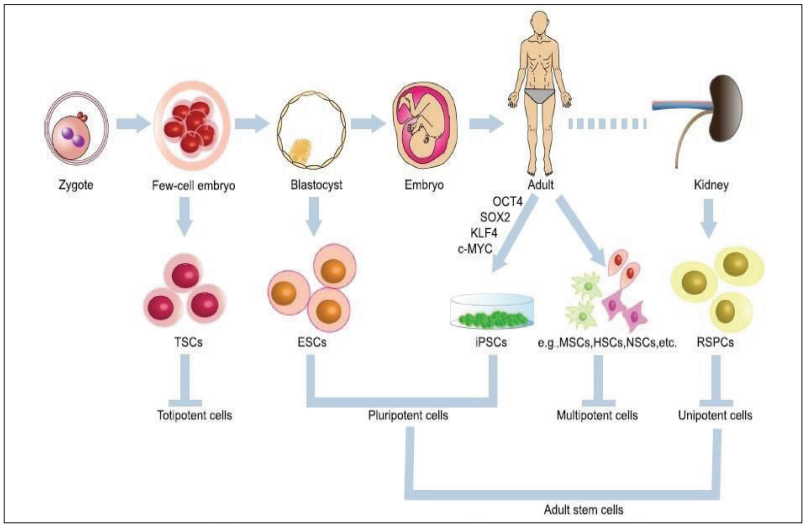
The following requirements must be met by stem cells before they can be used in clinical settings: they must be widely available (billions to billions of cells), non-invasive to obtain, able to differentiate into different cell types, and safe and effective when autologously transplanted (cell transplantation) to stem (stem cell transplantation for oneself) or allogeneic (stem cell expansion or production following Good Manufacturing Practices [GMPs] criteria) (Lindroos et al., 2011). Autologous stem cell therapy is the best type of stem cell therapy since it can lower the risk of rejection. Allogeneic stem cell therapy, on the other hand, has the potential to be therapeutic despite not coming from the patients themselves because it is simpler and more successful (Alwi, 2012; Hasanah & Nuban, 2021).

Stem cells can be classified into four categories based on their potential (Figure 1.1), as outlined below.

1) Totipotent stem cells can develop into embryonic and extra-embryonic (placental) cell types to generate an organism. The maximum capacity for cell differentiation is totipotent. This cell is created when sperm and egg cells combine to form a zygote.

These cells will grow into three germ layers (Zakrzewski et al., 2019).

2) Pluripotent stem cells can differentiate into embryonic cell types but not extra-embryonic tissue forms like the placenta. Comprising totipotent stem cells as their origin, these cells exhibit nearly limitless cell lineage potential, examples are iPSCs and ESCs (Amin et al., 2019; Liu et al., 2020; Zakrzewski et al., 2019).
3) Multipotent stem cells, such as hematopoietic stem cells, which can differentiate into many blood cell types, are cells that can differentiate into multiple cell types while remaining belonging to the same group. MSCs, neural stem cells (NSCs), and intestinal stem cells (ISCs) are further examples (Liu et al., 2020; Sobhani et al., 2017; Zakrzewski et al., 2019).
4) Unipotent stem cells possess the capacity to self-renew while only being able to develop into a single type of cell. Examples include renal stem cells, dermatocytes, and others (Balogh & Engelmann, 2011; Zakrzewski et al., 2019).



Source: Liu et al. (2020)

Figure 1.1 Potency of Differential of Stem Cells

Stem cells can be divided into three types: embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs).

1. Embryonic Stem Cells (ESCs)

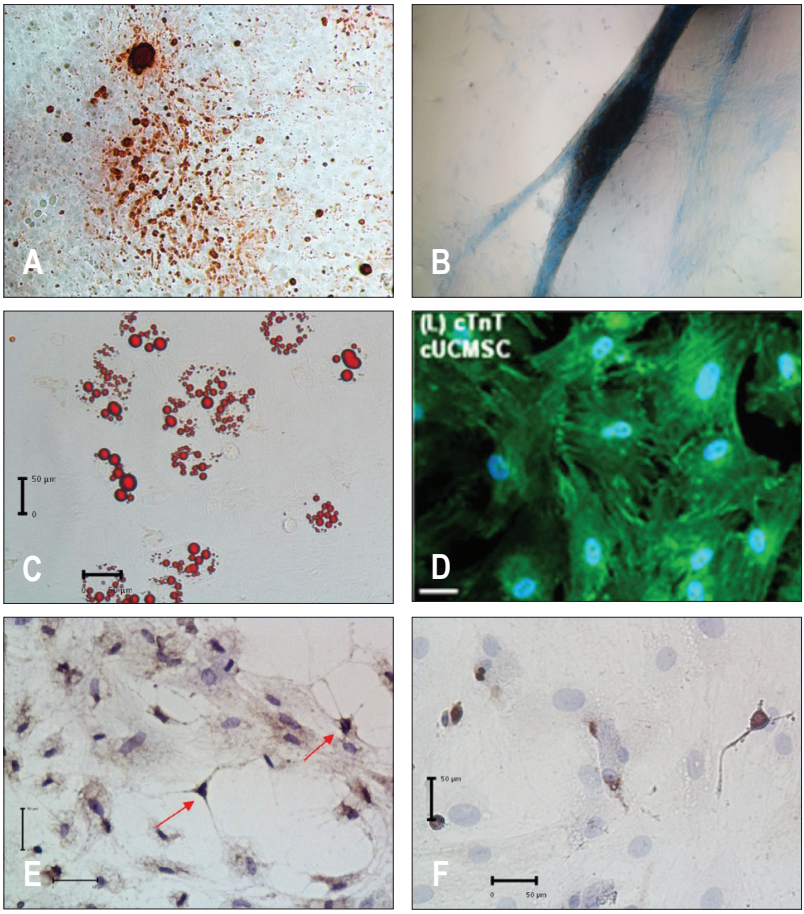
ESCs are derived from the blastocyst inner cell mass (ICM) stage, which is the early developmental stage of the embryo following 4–5 days of fertilization. These cells in the three germ layers—the ectoderm, mesoderm, and endoderm—are pluripotent, self-renewing, and able to develop into any kind of differentiated cell in the body (El Barky et al., 2017; Zhao et al., 2012).

2. Adult Stem Cells (ASCs)

Adult stem cells, also known as somatic stem cells, are undifferentiated cells present throughout the body. Adult stem cells can be obtained from bone marrow, fat tissue, peripheral blood, umbilical cord blood, Wharton's jelly, placenta, amniotic fluid, muscles, intestines, liver, kidneys, hair follicles, skin, blood vessels, urine, and menstrual blood. Only a small percentage of adult stem cells—such as those from umbilical cord blood—are pluripotent, while the majority are multipotent. Some are unipotent. MSCs and hematopoietic stem cells are two types of adult stem cells (Bacakova et al., 2018; S. Liu et al., 2016; Nguyen et al., 2016).

MSCs are a type of adult stem cells that can be obtained from bone marrow, adipose tissue, lung tissue, umbilical cord blood, peripheral blood, and other sources. The following criteria can be used to identify these stem cells, possess positive expression of CD73, CD90, and CD105, can adhere to plastic culture surfaces (plastic adherence) under standard culture conditions, able to differentiate into adipocytes, chondrocytes, and osteoblasts in vitro, does not express CD11b or CD14, CD19 or CD79α, CD34, CD45, and HLA-DR (Dominici et al., 2006).

Because of their multipotent characteristics, MSCs can develop into many types of cells. MSCs can differentiate in vitro into chondrocytes, osteoblasts, adipocytes, neurons, cardiomyocytes, and other cell types (Figure 1.2). In vitro, culture medium with growth factors is one common method for differentiating MSC utilizing



Notes: (A) Osteoblast; (B) Chondrocyte; (C) Adipocyte; (D) Cardiomyocyte (immunofluorecence – marker cTNT); (E) Neuron (imunocytochemistry - marker MAP-2); (F) Neuron (imunocytochemistry- marker Nestin).

Source: (A) & (B) Noviantari, Antarianto, et al. (2020), (C) Noviantari et al. (2023), (D) Hollweck et al. (2011), (E) Noviantari, Rinendyaputri, and Ariyanto (2020), (F) Noviantari, Antarianto, et al. (2020)

Figure 1.2 Differentiation Potential of MSCs

inducing factors (Huang et al., 2015; Macrin et al., 2017; Noviantari, Rinendyaputri, Yunindasari, et al., 2020; Taran et al., 2014).

The following tissues can be utilized for isolating MSCs.

1) The bone marrow

Bone marrow stem cells are also referred to as stromal cells. Bone marrow contains both hematopoietic and non-hematopoietic stem cells. Friedenstein first revealed in 1970 that there is a population of hematopoietic stem cells in femur bone marrow that attaches to plastic surfaces, whereas the majority of the cells are non-adherent. MSCs are these attached cells. The adhering cells multiply within a few days and, if grown in vitro, can develop into osteoblasts, adipocytes, and chondrocytes (Friedenstein et al., 1970; Morrison & Scadden, 2014; Pontikoglou et al., 2011).

MSCs from bone marrow compose a very small fraction of bone marrow, approximately 1 in 10,000 mononuclear cells (MNCs). Further research demonstrates the multipotency of these cells. These cells can develop into bone, cartilage, muscle, ligaments, tendons, dermis, and supporting tissue in addition to differentiating into osteoblasts, chondrocytes, and adipocytes (Caplan, 1991; Sandhaanam et al., 2013). The morphology of primary MSCs derived from rat bone marrow in Figure 1.3.

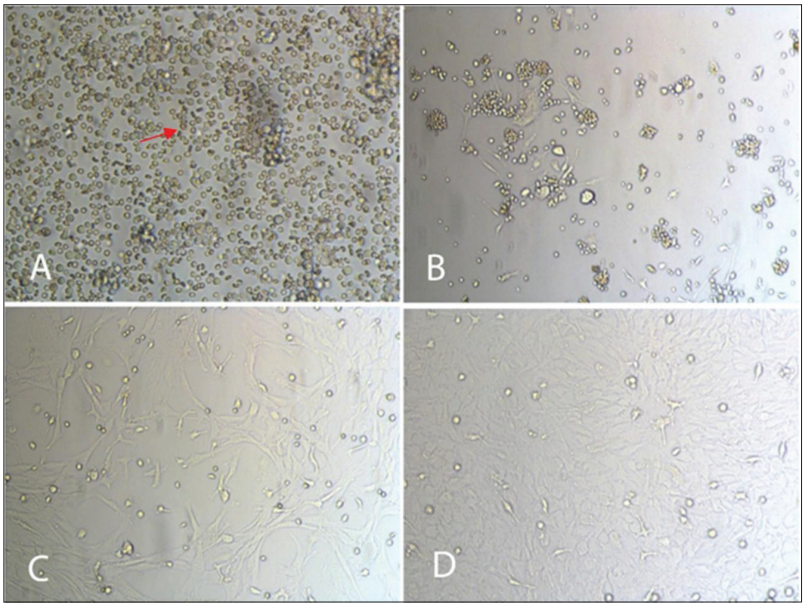
A variety of kinds of cells compose bone marrow stem cells. The expression of antigens on the cell surface is one of the characteristics noted. These bone marrow-derived MSCs express the hyaluronan receptor CD44, the transforming growth factor-b receptor III CD105, the thy-1 CD73, the melanoma cell adhesion molecule, or Mel-CAM, CD146, and do not express the hematopoietic cell markers CD11b, CD14, CD45, and CD34 (Pontikoglou et al., 2011).

2) Umbilical cord blood

The umbilical cord connects the fetus to the placenta. Furthermore, umbilical cord blood is a type of blood found in the placenta and

umbilical cord blood vessels. Three components make up the umbilical cord: Wharton's jelly, two arteries, one vein, and the cord lining (Figure 1.4) (Ali & Al-Mulla, 2012; Cassar & Blundell, 2016)

When compared to other stem cell sources, umbilical cord blood has the following advantages: it is simpler to obtain, does not threaten the donor, has low immunogenicity, reduces the risk of infection by cytomegalovirus or Epstein-Barr virus due to low placental transmission, and gives fewer ethical issues, minimal compared to stem cells from embryos. Umbilical cord blood stem cells do not require invasive treatments because they



Notes: (A) Rat bone marrow MSCs culture taken on day 0 (magnification 400x). Erythrocytes are shown by the arrow. Rat bone marrow MSCs culture on (B) day 1, (C) day 5, and (D) day 8 (B, C, D magnification 100x).

Source: Noviantari, Antarianto, et al. (2020)

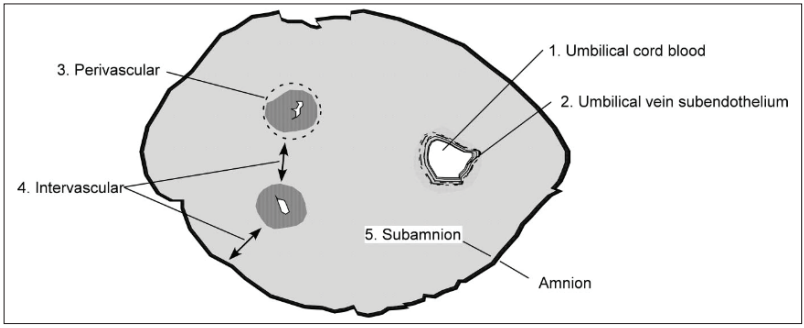
Figure 1.3 The Morphology of Primary MSCs Derived from Rat Bone Marrow

are derived from extraembryonic tissue, which is often removed during delivery. Despite their small quantity, umbilical cord blood stem cells possess the capacity to regenerate. This can be solved through cell expansion for clinical transplantation (Ilic et al., 2012; Yuliana et al., 2012).

3) Adipose tissue

One of the major organs in the body is adipose tissue. Thin adult women and men have between 3 and 4.5 kilograms of fat tissue in their bodies. Meanwhile, extremely obese people have about 45 kg of fat tissue (Halim et al., 2010). Adipocytes, fibroblasts, endothelial cells, vascular smooth muscle cells, and progenitor cells are some of the intricate constituents of adipose tissue (Lindroos et al., 2011).

After liposuction, adipose tissue is used to produce stem cells. Lipoaspirate may be processed right away or left unprocessed for up to three days before being processed again (Harris, 2014). It has been observed that bone marrow-derived stem cells and adipose tissue stem cells contain similar properties. Stem cells from adipose tissue have several advantages over those from bone marrow, including being easier to collect in large quantities, a low-risk and less painful technique, and easier cell replication.



Source: Troyer and Weiss (2008)

Figure 1.4 Anatomy of Umbilical Cord

In addition, these cells are immunosuppressive, simpler to get samples of adipose tissue, and can develop into other cells, including blood vessels. Thus, fat tissue stem cells hold great promise for regenerative therapy (Pawitan, 2009).

4) Wharton's jelly

Another source of stem cells is the gelatinous tissue called Wharton's jelly, known to be a component of the baby's umbilical cord. Stem cells from Wharton's jelly have several advantages, namely that they can be expanded or produced in large quantities, are easy to obtain, are not dangerous for donors both mother and baby, stemness properties can be maintained until passage 9–10, lower ethical problems compared to ESCs, and do not have the potential to develop to a tumor (Bagher et al., 2015).

5) Teeth

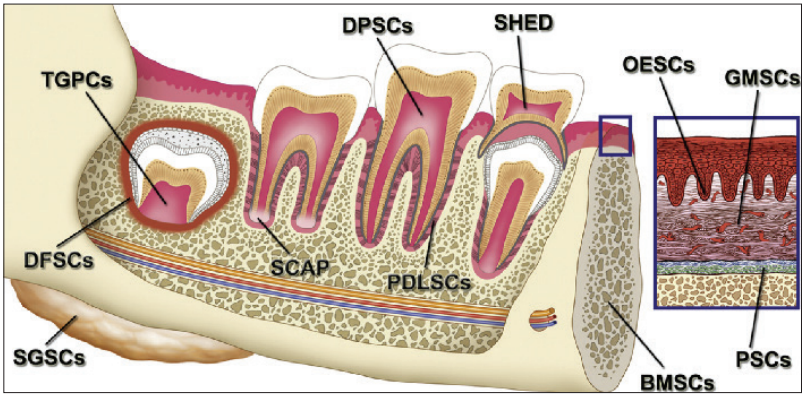
Stem cells can be obtained from teeth. Dental pulp stem cells (DPSCs) and human exfoliated deciduous stem cells (SHED) are two types of stem cells derived from teeth. Miura initially isolated SHED from a byproduct of extracting milk teeth. Because of this, there are an infinite number of stem cell sources available and the collection procedure is non-invasive. Other areas of the tooth (Figure 1.5) have sources of stem cells in addition to SHED and DPSCs (Egusa et al., 2012; Miura et al., 2003). SHED has a more effective proliferation potential than DPSCs and bone marrow-derived MSCs stem cells from teeth are also potential to differentiate into chondrogenic and osteogenic (Huang et al., 2009; Zakrzewski et al., 2019)

3. Induced Pluripotent Stem Cells (iPSCs)

Stem cells known as induced pluripotent stem cells (iPSCs) are produced by causing somatic cells to express characteristics similar to those of ESCs. To reprogram the somatic cell nucleus, exogenous

genes like OCT4, SOX2, NANOG, and LIN28 or OCT3/4, KLF4, and cMYC will be inserted. Using retroviral vectors to transduce the four transcription factors, OCT3/4, SOX2, KLF4, and cMYC are involved in the process of converting somatic cells into pluripotent iPSCs. Adult human somatic cells can be reprogrammed to become pluripotent, just as ESCs. In the future, iPSCs with this pluripotent quality may differentiate into any kind of adult cell, offering an alternative treatment for degenerative diseases (Takahashi & Yamanaka, 2013).

Since it was discovered that the transplanted cells mostly exerted their therapeutic impact through the secretion of paracrine substances, cell-free therapy has become a unique method in regenerative medicine over the past ten years. More and more data



Notes: BMSCs: bone marrow-derived MSCs;
DPSCs: dental pulp stem cells;
SHED: stem cells from human exfoliated deciduous teeth;
PDLSCs: periodontal ligament stem cells;
DFSCs: dental follicle stem cells;
TGPCs: tooth germ progenitor cells;
SCAP: stem cells from the apical papilla;
OESCs: oral epithelial progenitor/stem cells;
GMSCs: gingiva-derived MSCs,
PSCs: periosteum-derived stem cells;
SGSCs: salivary gland-derived stem cells.

Source: Egusa et al. (2012)

Figure 1.5 Sources of Stem Cells from Teeth

suggest that stem cell-derived secretomes, including growth factors, chemokines, cytokines, extracellular matrix (ECM), and extracellular vesicles (EVs), can repair wounded tissues as effectively as cells. This discovery has given rise to a novel concept for the use of secretome in regenerative medicine (Foo et al., 2021).

The secretome, referred to as the MSCs-conditioned medium (MSCs-CM), is a mixture of bioactive substances that have anti-inflammatory, anti-apoptotic, neuroprotective, and proliferative functions. Increasing data indicates that MSCs-CM plays a significant role in a variety of disorders, including bone, skin, muscle, and dental diseases. The conditioned medium includes growth and soluble factors like nerve growth factor (NGF), brain-derived nerve factor (BDNF), insulin growth factor (IGF); interleukin 10 (IL-10), tumor necrosis factor (TNF); and basic fibroblast growth factor (bFGF), that involved in neurogenesis and neuroprotection. The secretome can influence the differentiation of cells that retain their pluripotent or multipotent characteristics. Growth and neurotrophic factors from CM-rat bone marrow MSCs, such as bFGF and NGF, enhanced the ability of neural stem/progenitor cells (NPCs) to differentiate into astrocytes (GFAP) and neurons (NeuN) (Budiariati et al., 2021; Rinendyaputri et al., 2018).

C. Important Aspects of the Book

The previous section provided a brief overview of stem cells. The chapter is presented in an organized structure that facilitates the understanding of stem cells and their use in regenerative therapy. To this end, we would bring out that this book, *Discovering the Miracles of Stem Cell*, will discuss an in-depth comprehensive overview of the current state of stem cell research, including recent advances, challenges, and future directions, and contribute to filling such gaps by seeking contributions from researchers and practitioners interested in investigating the latest advances and challenges in stem cell research and its clinical applications. In summary, this book explores a wide spectrum of stem cell-related subjects that proceed from bench to bedside.

In Chapter 2, Jeanne Adiwinata Pawitan discusses "Stem Cells Culture Techniques: Mesenchymal Stem Cells". In this chapter, Pawitan has developed easy methods for establishing a culture of MSCs from the umbilical cord, bone marrow, and adipose tissue. These techniques involve a simple washing step with a filter for coffee, repeated harvest explant method, and simultaneous mononuclear cells (MNCs) separation followed by centrifugation. Pawitan also explains how to upscale culture, cryopreservation of MSCs, and aseptic technic to prevent MSCs culture contamination.

Ismail Hadisoebroto Dilogo in Chapter 3 discusses "Stem Cells for Orthopaedics Application". Dilogo describes that stem cells have shown a great deal of promise for promoting the regeneration of tendons, muscles, bones, and cartilage as well as for starting healing processes and making up for impairments in orthopaedics and trauma surgery. Among the many benefits of stem cell therapy include decreased pain, improved mobility and function, and tissue regeneration. Stem cell therapy for orthopaedic conditions has a promising success rate. Before its use can be broadly applied, its drawbacks—such as high cost, a lack of standardization, and restricted availability—must be resolved. Thus, we recommend more investigation, the creation of standardized procedures, the integration of tissue engineering and its methodology, and an in-depth study of the metabolites derived from stem cells, such as exosomes and secretomes.

Next, Siufui Hendrawan, Jennifer Lheman, David Victorious Lukas, and Sukmawati Tansil Tan discuss "Mesenchymal Stem Cells Secretome for Diabetic Wound". This chapter will focus on the potential use of stem cells in treating diabetes, including the differentiation of stem cells into insulin-producing cells and the transplantation of these cells into patients. As a diabetes alternative medicine, this one has a lot of promise and potential. New approaches, such as the use of encapsulated stem cells and nanotechnology, are required to overcome the limits of stem cells and their secretome to be

employed in a wide range of illnesses. Furthermore, expedited clinical applications necessitate collaboration between all parties involved.

After that, Winawati Eka Putri, Cita Rosita Sigit Prakoeswa discuss "Mesenchymal Stem Cells and Its Conditioned Medium: for Skin Aging". Putri et al. describe the application of conditioned medium and MSCs as a treatment for skin aging, for example from bone marrow, amniotic fluid or amniotic membrane, chorion, umbilical cord, umbilical cord blood, and adipose tissue. Recent research has shown that MSCs and CM of MSCs are safe to use. The high cost of manufacture and lack of standard operating procedures for creating stem cell conditioned medium are the limitations. More research is required to determine the best way to produce and give MSCs to optimize their anti-aging effects on the skin.

Teguh Santoso, Idrus Alwi, Cynthia Retna Sartika, Cosphiadi Irawan, Dewi Wulandari, Ika Prasetya Wijaya, Eka Ginanjar, Elizabeth Merry Wintery, Mohamad Syahrir Azizi, Aw Tar Choon, Bayu Winata Putera, Yanni Dirgantara, Angliana, Ditta Kalyani Devi, Nadya Karina, Rima Haifa, Nabilla Farah Naura, and Billy Yosua Costantin Pongajow discuss "Stem Cells for Acute Myocardial Infarction: Safety and Efficacy". This chapter explores the role of stem cells in development and regeneration, their use in therapy, and challenges. Santoso et al describe several factors that influence the success of stem cell therapy. Several potential influencing factors for the outcomes of allogeneic umbilical cord MSCs therapy (UC-MSCs) for ST-segment elevation myocardial infarction (STEMI) have been effectively found by the case series. To reach deeper conclusions, more investigation is necessary. Despite the noted notable improvements, the study's weaknesses include a small sample size of only four patients, which makes it difficult to generalize the findings.

Somia Gul, Saba Majeed, and Aisha Aziz discuss about "Stem Cells Based Therapies for Neurological Disorders". This chapter covers the potential use of stem cells in treating neurological disorders. Neurodegenerative diseases have a concerning side effect profile

when treated with traditional pharmaceutical therapy. For individuals with neurodegenerative diseases, stem cell therapy is currently most likely the most effective and desirable method of treatment. Stem cells have now been thoroughly tested in clinical settings for the treatment of a variety of neurological diseases, including Parkinson's disease, Alzheimer's disease, and others, having been studied in vitro and animal models.

Mochamad Syaifudin, Wimpie Pangkahila, Ida Sri Iswari, I Gusti Kamasan Nyoman Arijana, Basuki Supartono, and Mochamad Wildan in the next chapter discuss "The Potential of Cd34+ Hematopoietic Stem Cells to Increase Fibroblast and Collagen Skin in Ultraviolet B Exposed Skin". Syaifudin et al. describe that UV radiation can cause cellular component damage and photoaging caused by UV radiation can result in severe skin damage. Male Wistar rats that exposed to ultraviolet B (UVB) radiation showed an increase in fibroblasts and collagen in their skin following subcutaneous injection of human peripheral blood CD34+ stem cells.

Ahmad Faried and Yulius Hermanto discuss "Induced Pluripotent Stem Cells (iPSCs) and Neurological Diseases". The author explains that iPSCs were created using reprogramming technology, which allows researchers to examine cell fate decision mechanisms and model diseases in humans. It has provided novel possibilities for stem cell research and unique candidates in the pharmaceutical and clinical areas. iPSCs have potential use in toxicology, drug development, pathology, regenerative medicine, and the evaluation of pharmacological side effects. New insights into the biology of diseases and the possibility of developing novel therapeutics will be provided by the modeling of neurodevelopmental and neurodegenerative diseases.

Dito Anurogo discusses "The Art of Ethical Dimensions in Stem Cell Research". This chapter explores the ethical and regulatory considerations associated with stem cell applications. Anorogo describes that the study of stem cells has tremendous medicinal potential, but it also presents difficult ethical challenges, including

ESCs use. The complex rules and patents that impact research and affordability are part of the legal environment. Collaboration between researchers, ethicists, patients, and the general public is necessary to ensure a responsible approach and it is backed by international collaborations and ethical boards.

Finally, in Chapter 11, Basuki Supartono discusses "Stem Cells Are a New Hope, a New Horizon for Humanity and the Future of Human Beings: Representing Indonesia to the World". Supartono explains an overview of the development of stem cells in Indonesia, the role of the government in stem cell applications in the country, the limitations on stem cell research in Indonesia, and recommendations and suggestions for improving stem cell therapy in Indonesia.

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