Chapter 11

Stem Cells Are a New Hope, a New Horizon for Humanity and the Future of Human Beings: Representing Indonesia to the World

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A. Introduction

Numerous ailments—such as infections, traumas, degenerative conditions, malignancies, and congenital anomalies—have the potential to assail the human body, jeopardizing its survival. These illnesses can impact diverse systems, organs, tissues, and cells, culminating in structural impairments and functional disturbances. The integumentary, musculoskeletal, nervous, cardiovascular, endocrine, and other bodily systems may all be implicated. Failure to effectively manage these maladies can result in disability and mortality. Consequently, they engender myriad challenges and anguish for

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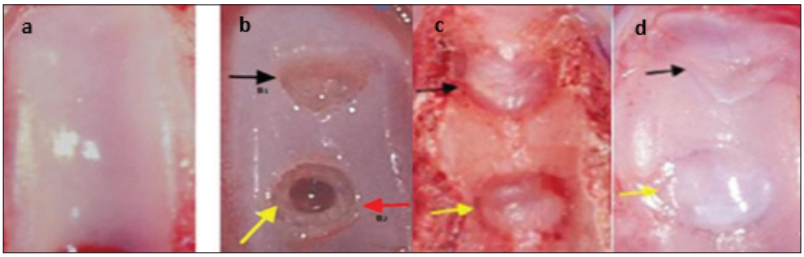
humanity, imposing burdens upon individuals, families, and societal and economic frameworks. Humanity endeavors to mitigate ailments via a multitude of strategies. However, not all interventions yield positive outcomes, with a fraction resulting in failure. Both medical and surgical therapies sometimes fail. Failure may occur because these therapies are unable to repair structures and restore tissue function to their original state (Supartono, 2018a).

Such failures can occur due to the nature and condition of the tissues themselves. Certain body tissues lack the capability for regeneration (healing). If these tissues experience structural disintegration and tissue dysfunction, they cannot heal because they are incapable of undergoing the healing process. An example of this is the cartilage tissue in knee joints. This tissue is avascular, meaning it lacks blood vessels, which results in the cartilage's inability to heal. When this tissue is diseased, injured, or aged, it cannot recover. In the event of knee joint cartilage damage, the regenerative response culminates in the formation of suboptimal, fibrous tissue. The quality of this tissue is not as good as the original tissue (Figure 11.1). To address this condition, the damaged tissue must be removed and replaced with artificial tissue made of metal and plastic materials. This procedure is known as joint replacement surgery. While offering therapeutic advantages, this surgical intervention is associated with



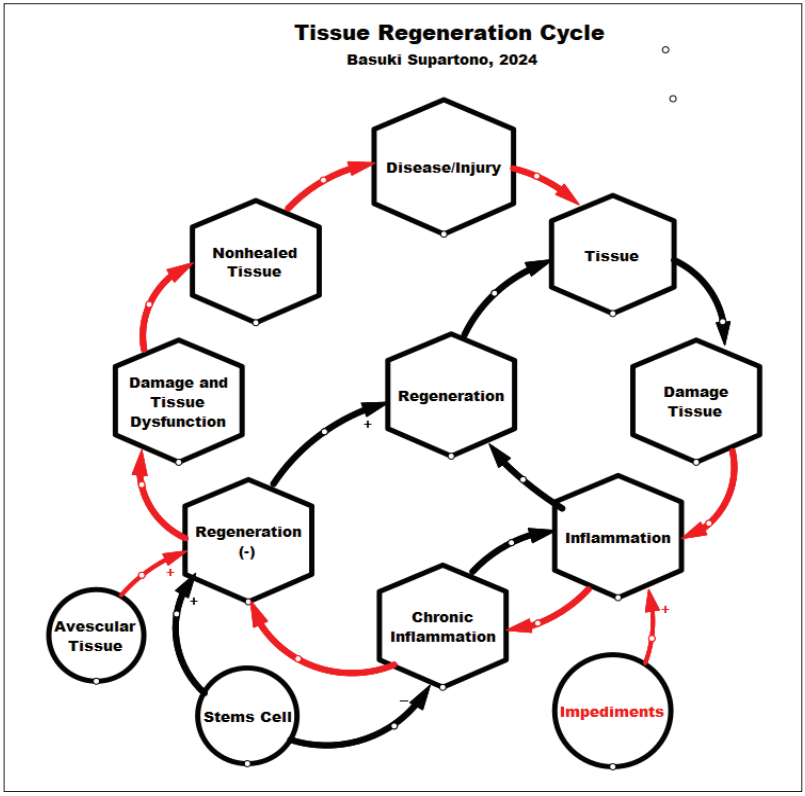
Notes: Knee joint cartilage of animals model: (A) normal cartilage, (B) cartilage defects, (C) 1 month after defects, (D) 2 months defects.

Source: Supartono et al. (2018)

Figure 11.1 Natural regeneration of cartilage defects in animal models results in fibrous tissue formation.

significant health risks and cannot fully re-establish the joint's original functional capacity (Supartono, 2018a).

Another factor contributing to healing failure arises from the impediments encountered by normal tissues during the regeneration process (Figure 11.2).



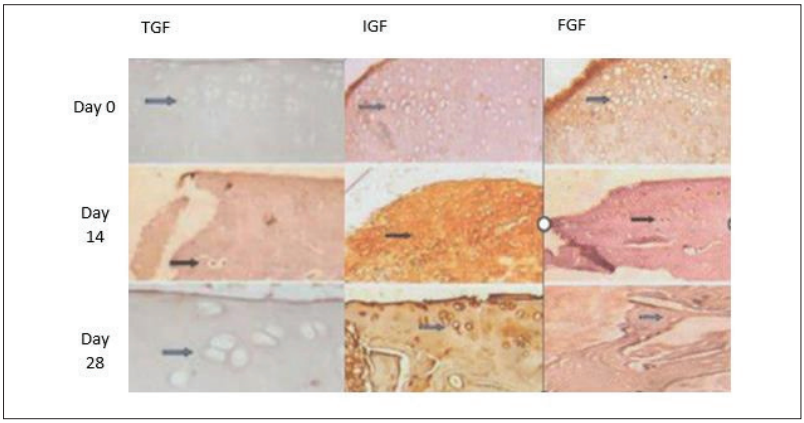
Notes: The normal tissue regeneration cycle consists of disease/injury, tissue damage, inflammation, and regeneration. Regeneration does not occur in avascular tissues and under conditions of chronic inflammation due to impediments caused by specific diseases. Stem cells play a role in modulating inflammation and act as agents of regeneration.

Source: Supartono (2023)

Figure 11.2 Tissue Regeneration Cycle

The healing cycle—encompassing tissue damage, inflammation, and regeneration—is disrupted, arresting at the inflammation stage. All normal tissues subjected to pathology, trauma, or senescence undergo damage, eliciting a counteractive inflammatory response from the tissue to mitigate the disturbance. This inflammatory phase is pivotal in establishing the requisite conditions for the onset of the regeneration phase

Our research shows that tissues affected by damage will respond with inflammation, release growth factors (GFs), and undergo tissue regeneration. These GFs are temporary and spatial. They appear after the first week, following the end of the inflammatory process, and persist for two weeks to stimulate cell formation. After two weeks, the GFs disappear to allow the restoration of the extracellular matrix and the formation of new, high-quality tissue (Figure 11.3) (Supartono, 2016b).



Notes: Tissue impacted by injury releases growth factors (GF) such as TGF, IGF, and FGF. These growth factors are temporary and act in a spatially specific manner. GFs emerge after the first week, following the conclusion of the inflammatory process, and persist for two weeks to stimulate cell formation. After two weeks, the GFs dissipate, allowing the restoration of the extracellular matrix and facilitating the formation of high-quality new tissue.

Source: Supartono (2023)

Figure 11.3 Tissue Regeneration Cycle

Nevertheless, under specific circumstances, the inflammatory response inadequately resolves the injury, persisting over an extended period and transitioning into chronic inflammation. A prototypical example is observed in wounds associated with diabetes, where prolonged hyperglycemia over years fosters an environment conducive to chronic inflammation, thereby inhibiting regenerative capabilities. Moreover, this chronic inflammatory state impedes the cellular and tissue regeneration processes, rendering the wound recalcitrant to healing or irreparable.

An additional determinant of tissue healing failure emanates from assorted pathologies, including degenerative conditions, malignancies, and traumatic injuries, all of which may precipitate chronic inflammation. Degenerative diseases and injuries have become a global health issue. Currently, degenerative diseases are among the top ten diseases in Indonesia (Dilogo, 2019). The cost burden of treatment is substantial, as seen in the treatments for diseases such as stroke, heart attack, and breast cancer (French & Emanuele, 2019). The incidence of trauma or injury is on an increasing trend (Supartono, 2014, 2015, 2016a). Injuries in the sports community, especially among athletes, pose a threat to their achievements and future prospects (Supartono, 2017). The aforementioned issues present a multifaceted and considerable challenge to public health, necessitating immediate remedial strategies. This scenario poses a substantial obstacle within the healthcare domain. Traditional medical and surgical interventions are often inadequate in fully addressing disease management. Consequently, there is an imperative need for an innovative methodology, specifically, a biological approach (Dilogo, 2019). A disease healing approach that accommodates the properties, characteristics, behavior of cells, and the regenerative capabilities of each tissue.

Efforts to address these issues have been pursued through a range of research endeavors, encompassing in vitro investigations, animal experimentation, and clinical trials, both globally and within Indonesia. Over the past decade, a novel medical approach has

emerged, termed interventional methodologies. This descriptor is apt as it involves direct intervention at the cellular level. Alternatively known as tissue engineering techniques, this methodology involves the modification of diseased tissues to generate healthy, functional replacements. This approach holds promise in addressing diseases that have historically posed significant treatment challenges. Furthermore, it can be executed without resorting to surgical procedures, thereby reducing costs and mitigating the risks of complications, disabilities, and mortality. The advent of this methodology presents a fresh and hopeful avenue for disease management and the evolution of healthcare (Supartono, 2023).

B. Tissue Engineering Technique

Tissue engineering harnesses the properties of tissues and the capabilities of engineering components. Its implementation involves employing three primary engineering components: cells, signaling molecules, and scaffolds. A scaffold is an artificial environment conducive to cellular growth and maturation, facilitating the maintenance of cellular life cycles, proliferation, differentiation, and extracellular matrix production. Scaffolds can be fashioned from natural, synthetic, or hybrid materials, playing a pivotal role in the efficacy of tissue engineering endeavors. Signaling molecules, also known as growth factors (GFs), are compounds capable of eliciting cellular responses and promoting extracellular matrix synthesis. In contemporary practice, scaffolds and growth factors are readily available in pharmaceutical formulations. Tissue engineering methodologies entail the integration of all three engineering components. However, they can also be implemented using individual components. Monocomponent applications predominantly involve the utilization of cells, specifically responsive cells capable of proliferation and the formation of cellular and tissue matrices.

At first, healthy cells sourced from the target tissue were utilized. These cells are terminally differentiated, signifying that they have assumed specific morphological and functional characteristics. For

instance, mature chondrocytes harvested from cartilaginous tissue are cultured in vitro before being transplanted into damaged tissues to facilitate tissue regeneration. However, this approach encounters numerous challenges and limitations. The process necessitates several sequential stages, including cell isolation, cultivation, and implantation. Cell collection involves surgical interventions that are discomforting, costly, and associated with inherent morbidity risks. Furthermore, the quantity of harvestable cells is restricted, and their quality is contingent upon the patient's age and health status. Moreover, the harvesting process carries the risk of structural damage and diminished cellular functionality, leading to the formation of low-quality regenerative tissue (i.e., scar tissue). Consequently, the utilization of such cells has been largely discontinued. In pursuit of a more promising alternative, researchers, scientists, and clinicians have shifted their focus to stem cells, owing to their capacity to generate high-quality tissue structures and functions. Additionally, the procedure is less invasive and can be performed without resorting to surgical interventions (Supartono, 2018a).

C. The Role of Stem Cells in Tissue Regeneration

In human, illnesses and injuries can inflict harm upon cellular and tissues. To prevent the disruption of physiological functions, the restoration or substitution of this damage is imperative. Stem cells, ubiquitous in human tissues, fulfill this vital function. This provision, bestowed by the Divine in His benevolence, underscores the significance of these cells for human welfare. Tissue-specific stem cells possess both inherent and adaptive qualities, ensuring their capacity to engage in tissue repair endeavors exclusively when necessitated.

Cell division is achieved through symmetric division, producing two identical totipotent daughter cells. Additionally, asymmetric division occurs to produce one identical stem cell and one progenitor cell. Each progenitor cell generates another progenitor cell like itself and another cell that begins the determination process to form a specific cell according to tissue needs. Progenitor cells grow and

develop according to commitment and organize themselves within the tissue architecture. In summary, it can be said that everybody tissue contains stem and progenitor cells with the capability to grow and develop as required by life's demands (Supartono, 2018a).

The Capabilities of Stem Cells and the Plasticity of Tissue Stem Cells

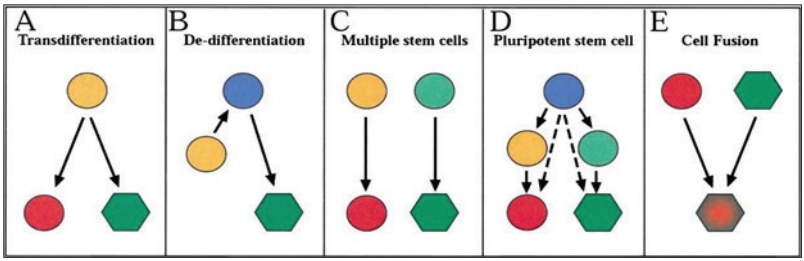
Stem cells exhibit varying degrees of developmental potential based on the exigencies of their tasks and roles. These developmental capacities encompass totipotency, pluripotency, multipotency, oligopotency, and unipotency. Totipotency denotes the unrestricted capacity of stem cells to generate all types of bodily tissue cells, encompassing both embryonal and extra-embryonal tissues, as well as to engender new organisms. Embryonic stem cells and germ layer stem cells exemplify this capability.

Pluripotency denotes the capacity to generate all types of body cells, including germ cells and certain extra-embryonal tissues, albeit without the ability to form a new organism. Multipotency signifies the capacity to generate numerous types of adult cells within the same lineage. Oligopotency denotes the capacity to generate a limited number of adult cell types. Unipotency refers to the capacity to generate a single type of adult cell. These developmental potentials are influenced by various factors, such as the stem cell type, genetic attributes, cell culture conditions, growth factors, microenvironmental cues, and cellular interactions

Furthermore, tissue stem cells demonstrate inherent plasticity, defined as the capacity to differentiate into cell types distinct from their lineage of origin. This characteristic is observable across stem cells from a diverse array of organs and tissues, including but not limited to the liver, pancreas, nervous system, brain, epidermis, bone marrow, muscular tissue, synovial membrane, and hematopoietic system. Within the hepatic environment, oval cells have the potential to differentiate into epithelial cells of the bile ducts. The pancreas harbors multipotent precursor cells, which, while akin to progenitor

cells, exhibit a marginally reduced differentiation potential. These pancreatic precursors are competent in giving rise to both pancreatic endocrine and exocrine cells, as well as neuronal cell types. Similarly, neural stem cells possess the plasticity to differentiate into progenitor cells of the hematopoietic lineage, myocytes, cells of the germ layers, and mesodermal cells. Peripheral blood stem cells have been demonstrated to differentiate into endothelial cells, osteoblasts, and chondrocytes. Notably, Supartono et al's research elucidated that CD34+ hematopoietic stem cells are capable of transdifferentiating into chondrocytes, thereby contributing to the formation of joint cartilage tissue. The plasticity inherent to tissue-specific stem cells heralds a paradigm shift in the approach to the treatment of various diseases (Supartono et al., 2018).

Supartono (2018a) postulated that the plasticity observed in stem cells can be attributed to multiple underlying mechanisms, which include (a) transdifferentiation, (b) dedifferentiation, (c) existence of dual-potency stem cells, (d) pluripotency of certain stem cells, and (e) cell fusion, as illustrated in Figure 11.4. Transdifferentiation refers to the process whereby tissue-specific stem cells undergo a phenotypic



Notes: Mechanisms of stem cell plasticity include (A) transdifferentiation, (B) dedifferentiation, (C) multiple stem cells, (D) pluripotent stem cells, and (E) cell fusion. Tissue stem cells: orange or green spheres; pluripotent cells: blue spheres; orange lineage differentiation cells: red spheres, and green lineage differentiation cells: green hexagons.

Source: Supartono (2018a)

Figure 11.4 Schematic Diagram of the Mechanism of Tissue Stem Cell Plasticity, from Waggers

conversion, resulting in the emergence of cell types divergent from their original lineage. This capacity for transdifferentiation is contingent upon the microenvironment of the resident tissue. For instance, stem cells residing within the bone marrow or circulating in the peripheral blood have the ability to give rise to cell types unrelated to hematopoietic lineage.

Furthermore, both hematopoietic and mesenchymal stem cells within the bone marrow possess the remarkable capacity to migrate to distinct tissue sites, undergoing cellular transformation to adopt the characteristics of the resident tissue cells. Dedifferentiation describes a process whereby tissue-specific stem cells regress to a more primordial or multipotent state, thereby acquiring the capability to differentiate into cell types of a novel lineage. The phenomenon of dual stem cells refers to the capacity of tissue-specific stem cells to simultaneously generate a progenitor cell akin to their original form as well as progenitor cells destined for differentiation into alternate lineages. Pluripotent stem cells embody a transformative mechanism through which tissue-specific stem cells attain pluripotency, facilitating the emergence of dual progenitor cells and, subsequently, divergent lineage pathways. Cell fusion encompasses a process by which two tissue-specific stem cells amalgamate, culminating in the genesis of a distinct cellular entity (Supartono, 2018a).

D. Stem Cells and Their Applications in Tissue Engineering Techniques

Stem cells, inherently undifferentiated, boast the capacity for self-replication and renewal. Through the synthesis of the author's research alongside contributions from other scholars in the field, it has been elucidated that stem cells exhibit three primary functions: modulation of inflammatory responses, facilitation of tissue repair and regeneration, and suppression of microbial proliferation. These intrinsic properties present viable avenues for therapeutic applications. Under certain pathological or traumatic scenarios, an individual's endogenous stem cell reservoir may prove inadequate, attributed

either to a paucity in cell quantity or a decrement in functional quality. In such instances, the clinical scenario may necessitate the exogenous administration of stem cell-derived products to augment or restore the body's reparative and regenerative competencies.

Legislative mandates within Indonesia expressly prohibit the application of embryonic stem cells in clinical settings, permitting instead the utilization of non-embryonic, or alternately termed, tissue-derived stem cells from human sources. Such tissue stem cells are ubiquitously distributed throughout various bodily tissues, encompassing both germinal and somatic cell populations. From a technical perspective, these cells are identifiable within both solid tissues—exemplified by skin, adipose tissue, placenta, muscular tissue, and synovial membranes—and fluidic matrices, including bone marrow aspirate, umbilical cord blood, and peripheral circulatory system. Characterization of tissue stem cells facilitates their classification into several key categories: progenitor or mononuclear cells, mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs). These stem cells are harvested from an array of tissues originating from either the patient or a donor (Supartono, 2023).

1. Tissue Stem Cell Production

The production of tissue stem cells within Indonesia holds the potential to diminish reliance on foreign pharmaceutical imports, thereby enhancing national self-sufficiency. The process begins with the isolation of mononuclear progenitor cells, which are then cultured or expansion into various types of stem cells with the desired characteristics (Supartono, 2018a).

2. Techniques and Procedures of Tissue Stem Cell

The production of stem cells encompasses a series of sophisticated steps, including cell isolation, cell characterization, selection, in vitro culture, cell expansion, cryopreservation, cryogenic storage, and subsequent thawing. These processes have been conducted

Notes: (A) manual tissue stem cell processing in the laboratory, (B) a stem cell processing machine.

Source: Supartono (2023)

Figure 11.5 Processing of the Tissue Stem Cells

manually. However, advancements in biotechnology have facilitated their automation. Stem cell processing machines are now available (refer to Figure 11.5). These devices are capable of converting human blood or bone marrow aspiration into assorted stem cell types through an enclosed, sterile system, ensuring the production of clinical-grade products ready for direct patient application. Such machinery offers a cost-effective solution for the large-scale production of diverse stem cell products, catering to broad therapeutic needs. The cells thus processed may be cryopreserved for future use or immediately deployed in therapeutic interventions (Supartono, 2023).

3. Laboratories for Stem Cell Processing

In accordance with prevailing Indonesian regulations, stem cell production is mandated to occur within laboratories specifically designated for stem cell research and processing. There are two types of these laboratories: research laboratories that produce stem cells for research purposes and Laboratories for Stem Cell Processing for Clinical Application (commonly referred to as LPSAK in Indonesian) for producing stem cells for patient treatment.

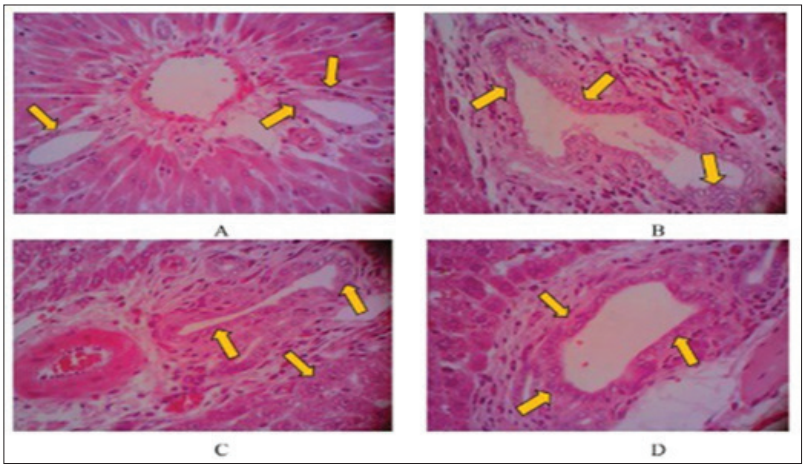
LPSAK must follow the prevailing government regulations and are supervised by the Ministry of Health of the Republic of Indonesia, the Food and Drug Monitoring Agency of the Republic of Indonesia, and the Indonesian Stem Cell Committee. These regulations are outlined in the Minister of Health Regulation of the Republic of Indonesia Number 50 of 2012 regarding the Operation of Stem Cell Processing Laboratories for Clinical Applications (Permenkes No. 50, 2012).

4. Stem Cell Applications

The application of stem cells can be administered through various routes, including topical, intravenous, intra-arterial, intramuscular, and other routes. Once introduced into the host organism, these cells persist, proliferate, and differentiate within the recipient's milieu. Such cells engender the formation of novel cells and tissues, facilitating the repair of tissue degradation and the restoration of tissue functionality to its baseline condition. Consequently, organ and systemic functions are reinstated to their normal states, culminating in the recovey of the patient's health (Supartono, 2018a). The use of stem cells in surgery can save time, reduce complications, shorten the duration of surgery, and provide good outcomes (Dilogo, 2019). However, their implementation must be safe, beneficial, comfortable, efficient, and cost-effective.

5. Safety of Tissue Stem Cells

Stem cell applications have the potential to elicit rejection reactions, thus requiring an evaluation of their safety. Research has shown that the application of tissue stem cells is safe, without causing rejection or toxic reactions. Several studies have documented this. Basuki found that the administration of human hematopoietic stem cells (HSCs) to animal models is safe and does not provoke rejection or toxic reactions (Supartono, 2017). Another study by Supartono showed similar results.



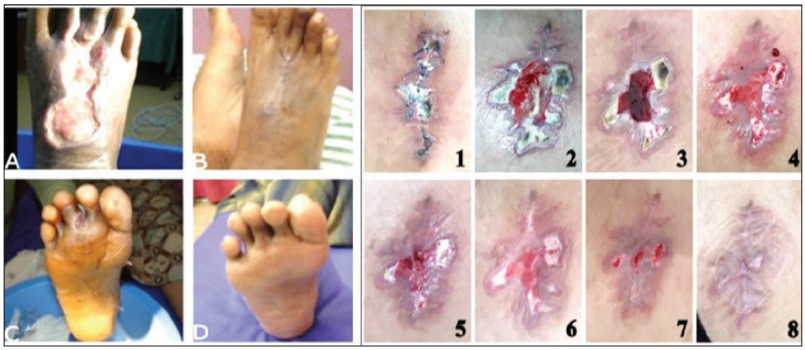
Notes: The number of cells in the bile duct has increased in all of the treated groups compared to the control group, as shown by yellow arrows. The shape of the cells in the treated groups looked more oval than the control group. (A) control, (B) 105 cells, (C) 106 cells, (D) 107 cells.

Source: Supartono et al. (2022)

Figure 11.6 Microscopic Images Of Tissue Regeneration (Oval Cells) in Naive Rats Following Repeated Intravenous Injections of Human PBMC Once a Month for Three Months

The monthly intravenous administration of human progenitor cells (PBMC) to animal models for three months was found to be safe, without any rejection or toxic reactions. The animals remained healthy clinically, in laboratory tests, and histopathologically. Moreover, it was demonstrated that the procedure did not interfere with and still induced tissue regeneration—see Figure 11.6 (Supartono et al., 2022).

Supartono (2018b) reported that the weekly administration of peripheral blood mononuclear stem cells (PBMC) from both patients and donors for two months has been proven safe. There were no



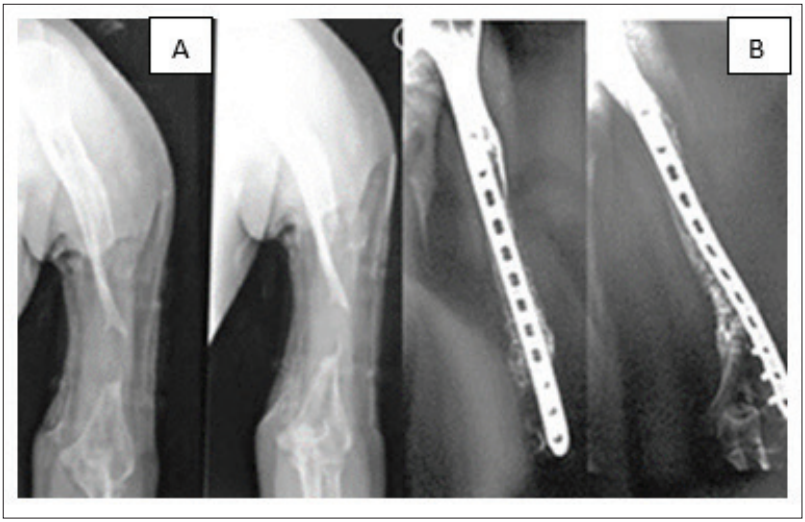
Notes: Figure A, B, C and D describes the weekly administration of peripheral blood mononuclear cells (PBMC) from patients and donors (described by figure 1–8) for two months that has been proven safe. There were no signs of rejection reactions, allergic reactions, infection, toxic reactions, or complications. It aids in the regeneration process or healing of chronic (banal) diabetic wounds that are difficult to heal.

Source: Supartono (2018b)

Figure 11.7 Safety of Administration of Peripheral Blood Mononuclear Cells (PBMC) to Patients with Unhealed Diabetic Wounds

rejection reactions, allergic reactions, signs of infection, toxic reactions, or any adverse complications. Contrary to inhibiting, these interventions facilitated the regenerative process, significantly promoting the healing of chronic, banal diabetic wounds—see Figure 11.7 (Supartono, 2018b).

The application of mesenchymal stem cells (MSCs) and their metabolic products has been proven safe. Ismail reported that the administration of mesenchymal stem cells (MSCs) to patients with bone defects at Cipto Mangunkusumo Hospital in Jakarta was proven to be safe. Furthermore, the application of these stem cells, whether from patients or donors, had a positive impact on the bone regeneration process (Figure 11.8; Dilogo et al., 2019).



Description: The application of mesenchymal stem cells (MSCs) from both patients and donors in patients with bone defects has been proven safe and positively impacts bone regeneration processes. (A) before administration, (B) after administration.

Source: Dilogo et al. (2019)

Figure 11.8 Safety of Administration of Mesenchymal Stem Cells (MSCs) to Patients with Critical Bone Defects

6. Legal Aspects of Stem Cell Services in Indonesia

Indonesia accommodates stem cell-based therapy. The Government of the Republic of Indonesia, through the Health Law No. 17 of 2023, states that stem cells can be used for disease treatment and health recovery (UU No. 17, 2023). Stem cell therapy is primarily directed towards humanitarian objectives, eschewing commercial exploitation. Its application is strictly non-reproductive and contingent upon rigorous validation of its safety and therapeutic efficacy. Moreover, this therapeutic modality is obligated to adhere to established healthcare service protocols, whilst duly acknowledging and integrating societal roles, socio-cultural norms, moral principles, and ethical standards. Details on this matter are regulated in the Minister of Health

Regulation No. 32 of 2018 on the Provision of Stem Cell Services (Permenkes No. 32, 2018).

Stem cell therapy can be administered for degenerative diseases, non-degenerative diseases, and the rejuvenation of cells, tissues, and organs. The source of these stem cells may be autologous or allogeneic, provided voluntarily and without financial remuneration. The types of stem cells that can be administered include mesenchymal stem cells, hematopoietic stem cells, progenitor cells, and secretome.

The secretome is a stem cell product containing growth factors, cytokines, and microvesicular structures, exosomes, and other factors. Stem cells and secretomes must meet quality, safety, efficacy requirements, and have marketing authorization.

Clinical applications of stem cells, whether systemic, regional, local, or topical, are performed by competent medical personnel in hospitals and clinics in accordance with applicable regulations. Clinics are only allowed for local and topical applications. The use of stem cells is carried out in the form of standardized therapy services, the standards of which are set by the Minister of Health of the Republic of Indonesia. Other uses include research-based therapy services organized in hospitals designated by the Minister of Health of the Republic of Indonesia. Hospitals or clinics can set and charge for standardized therapy services or replacement costs for processing in research-based therapy services. Costs incurred from the use of stem cells can be covered by the patient, grants from the central government, local government, research institutions, and donations from the community (Permenkes No. 32, 2018).

7. Religious Aspects of Stem Cells

Indonesia guarantees its citizens the right to worship and practice their religious teachings. In accordance with the constitutional mandate, the state provides protection and assurances regarding the halal status of products utilized by the community through Law No. 33 of 2014 on Halal Product Assurance. The Government of the Republic of Indonesia provides legal certainty in the form of Halal

Product Assurance, evidenced by a Halal Certificate (UU No. 33, 2014). On September 9, 2020, the Indonesian Ulema Council issued a fatwa as a guideline for the government, medical personnel, and the public regarding the use of stem cells. The Indonesian Ulema Council requested the government to strictly supervise stem cell therapy providers and urged medical personnel to always consider the sharia aspects in every medical action. The law on the use of stem cells is twofold: haram (forbidden) or *mubah* (permitted).

The use of human stem cells for any purpose is fundamentally haram if the source of the cells is taken in a manner not in accordance with legal stipulations. Other reasons for being haram include (a) if the extraction of stem cells causes hardship (*masyaqqah*) or harm (*dharar*) to the donor or recipient; (b) if their effectiveness is still in doubt; (c) if used to alter the natural shape of the body to make it more attractive, change identity, or for other purposes that contradict sharia; (d) if stem cells are bought and sold between the cell owner and another party; and (e) for reproductive purposes (to create a new being). Based on the preceding discussion, the administration of human tissue-derived stem cells is permitted for therapeutic treatments, tissue regeneration, and medical research purposes, contingent upon obtaining written consent from the donors (Fatwa Majelis Ulama Indonesia No. 51, 2020).

8. The Use of Stem Cells in Indonesia

As mentioned above, the use of stem cells in Indonesia has been proceeding through research-based therapeutic services. The use of these stem cells is articulated engagingly throughout the chapters of this book. Titled *Discovering the Miracles of Stem Cells*, the book unveils the extraordinary potential of stem cells. Leading stem cell researchers from various research centers in Indonesia report on a range of research findings about the potential and use of tissue stem cells. This includes discussions on the processing of mesenchymal stem cells, induced stem cells, the potential of stem cells for neurological diseases, and the ethical aspects of tissue stem cells. Additionally,

it explains the use of mesenchymal stem cells and their metabolic products for the treatment of orthopaedic diseases, diabetes, skin rejuvenation, and myocardial infarction. Of particular interest is the potential for hematopoietic stem cells to transdifferentiate into skin-forming cells and tissues.

This book is highly engaging as it elucidates the position and contribution of Indonesian stem cell scientists in the scientific journey to discover the potential and benefits of stem cells. It reveals the role of Indonesian scientists in building a golden bridge toward achieving a future of high-quality health life.

9. Bridging the Future

Currently, we stand on the cusp of a new epoch in the fields of medicine and biotechnology, thereby underscoring the importance of contemplating the extensive journey embarked upon in "Discovering the Wonders of Stem Cells". Beginning with innovative techniques in stem cell culture, potential and benefits, to the ethical debates surrounding stem cell research. Each chapter has unveiled various challenging and promising aspects of stem cells.

Jeanne Adiwinata Pawitan elaborated on methodologies for the isolation, culture, and cryopreservation of mesenchymal stem cells (MSCs), highlighting the significance of meticulous sample management and isolation protocols to enhance therapeutic outcomes. Various techniques are utilized to extract MSCs from adipose and umbilical cord tissues, each presenting distinct benefits and considerations. The expansion of MSCs cultures necessitates the adoption of alternative systems, such as hollow fiber systems and hyperflasks, to efficiently accommodate large-scale production requirements. Cryopreservation strategies, inclusive of alternatives to the conventional dimethyl sulfoxide (DMSO)-based solutions, are critical for ensuring the prolonged viability of MSCs without degrading their quality. The application of aseptic procedures is essential to mitigate contamination risks throughout the isolation and culturing phases. The evolution of MSC culture methods, cryopreservation

techniques, and aseptic protocols has significantly contributed to the establishment of effective procedures vital for both research and therapeutic applications. Acquiring proficiency in these techniques is crucial for the successful production of MSCs. Pawitan has introduced cost-effective strategies for the generation of MSCs from bone marrow, adipose, and umbilical cord tissues, which are compatible with current Good Manufacturing Practices (GMP) in laboratory settings.

Ismail Hadisoebroto Dilogo explained thoroughly, the use of stem cells in orthopaedics has surged in the past decade, driven by advances in scientific research. Stem cells offer potential for regenerative medicine in treating bone abnormalities and regenerating tissues like nerves, tendons, ligaments, and cartilage. Mesenchymal stem cells (MSCs) are commonly used in orthopaedic disorders due to their differentiation potential. Clinical studies, particularly in neurology and orthopaedics, have highlighted the prominence of MSC-based therapies. MSCs play a vital role in fracture repair by promoting angiogenesis and bone regeneration, offering promising solutions for non-union fractures.

In treating articular cartilage defects, stem cell-based therapies, including exogenous MSCs and their secretome, show potential in enhancing cartilage repair and slowing or reversing cartilage damage. Research into exosomes derived from MSCs also holds promise in cartilage regeneration by boosting cell proliferation, reducing inflammation, and enhancing cartilage repair. Overall, stem cell-based approaches hold considerable promise for orthopaedic disorders, with ongoing research aimed at optimizing their therapeutic potential and overcoming existing challenges.

Siufui Hendrawan et al. have shown that secretome-based therapy, derived from mesenchymal stem cells (MSCs), exhibits potential in treating diabetic wounds. The secretome provides a cell-free option that possesses lower immunogenicity. Future prospects involve addressing challenges in secretome therapies to expand their clinical applications. Despite facing obstacles, these therapies offer promising alternatives for the treatment of diabetic wounds.

Winawati Eka Putri and Cita Rosita Sigit Prakoeswa have revealed that mesenchymal stem cells (MSCs) have attracted significant attention for their potential in rejuvenating aged skin, attributed to their regenerative capabilities. Research has demonstrated encouraging outcomes of MSC-derived conditioned medium (MSC-CM) in wound healing, photoprotection, and enhancing clinical indicators of skin aging. Various sources of MSC-CM, including bone marrow, umbilical cord, amniotic fluid, adipose tissue, and chorion, have been investigated for their therapeutic impacts on aged skin. Methods of application generally encompass subcutaneous injections or microneedling techniques. Although adverse effects are rare, careful measures should be adopted to prevent complications. Collectively, MSCs and MSC-CM offer promising pathways for the treatment of skin aging, providing potential advantages in tissue regeneration and rejuvenation.

Teguh Santoso et al. have reported the results of their clinical trials on the exploration of stem cell therapy›s efficacy in treating ST-segment elevation myocardial infarction (STEMI) and its aftermath. Stem cell therapy emerges as a promising avenue for replacing or repairing damaged cardiac tissue, with factors like the stem cell source, administration route, dosage, preparation, and timing critically affecting its success. Mesenchymal stem cells derived from the umbilical cord (UC-MSCs) have demonstrated potential in cardiac regeneration owing to their paracrine effects and minimal immunogenicity. Clinical trials employing intracoronary and intravenous administration methods have yielded positive outcomes, including enhancements in left ventricular function and patient quality of life. Despite challenges such as limited sample sizes, stem cell therapy presents a viable strategy for alleviating the detrimental impacts of STEMI and enhancing patient prognosis, underscoring the need for further research to refine its application.

Mochamad Syaifudin et al. have demonstrated the potential for transdifferentiation of CD34+ cells into skin cells and tissues. The characteristics and potential of hematopoietic stem cells, specifically

CD34+ cells, in enhancing fibroblast and collagen production in UV-exposed skin are investigated. The plasticity of HSCs allows them, under certain conditions, to aid in tissue regeneration beyond the blood system, opening avenues for regenerative therapies.

The text delves into several facets of hematopoiesis, including the proliferative behavior of HSCs, modes of cell division, examples of tissues illustrating stem cell functions, and the therapeutic applications of stem cells in combating skin aging. It highlights the crucial role of HSCs in tissue regeneration. Moreover, the text examines the molecular mechanisms behind HSC differentiation and the importance of CD34+ hematopoietic stem cells in skin rejuvenation, particularly their role in boosting fibroblast and collagen production. Mochamad Syaifudin calls for additional research to confirm these results and refine treatment methodologies for clinical use.

Somia Gul et al. theoretically discuss how stem cells therapy presents a promising avenue for addressing neurodegenerative diseases by facilitating neuronal regeneration and correcting abnormalities in neuronal circuitry. Stem cell therapy has the potential to repair hippocampal circuits, improve patterns of cognitive and emotional behavior, and treat neurodegenerative disorders, such as Alzheimer's disease. Despite the associated risk factors and limitations, stem cell therapy has demonstrated promising results in various conditions, including ischemia-induced diseases, gliomas, and spinal cord injuries. Continuous research and technological developments are anticipated to enhance outcomes in the future.

Ahmad Faried and Yulius Hermanto delve theoretically into the depth of induced pluripotent stem cells (iPSCs). The document details the process of nuclear reprogramming to generate iPSCs, emphasizing their potential applications in regenerative medicine. The text proceeds to examine the modeling of neurological disorders using iPSC-derived neural cells. Various neurological diseases, such as Parkinson's disease and Alzheimer's disease, are referenced, alongside the challenges of modeling these conditions with iPSC-derived neural cells. Overall, the document offers an exhaustive review of

the creation, significance, and utility of induced pluripotent stem cells in neurological disease research and treatment. Moreover, the document discusses the prospects of iPSC-based therapies for neurological disorders. Although stem cells therapy shows promise, it faces obstacles, such as challenges in somatic cell reprogramming, genetic alterations, and the necessity for comprehensive preclinical evaluations.

Finally, Dito Anurogo underscores the ethical issues inherent in stem cell research and application. Stem cell research harbors significant potential to transform medicine and biotechnology, providing prospective treatments for various severe conditions through regenerative therapies. Nonetheless, the ethical quandaries associated with the sourcing of stem cells remain a central concern. Paramount to this discussion is the principle of informed consent, particularly in the context of stem cell clinical trials, where the risks and benefits must be transparently communicated to participants. Moreover, adherence to ethical guidelines and best practices is crucial for the responsible conduct of stem cell research. In Indonesia, ethical considerations blend international norms with local cultural and religious values, highlighting the importance of collective well-being while respecting individual autonomy. As stem cell research progresses, the advent of new technologies such as organoid development and gene editing introduces additional ethical challenges. This necessitates continuous ethical reflection to ensure responsible innovation and the protection of human dignity.

At the culmination of the scientific endeavor *Discovering the Miracles of Stem Cells*, it is imperative to deeply explore the essence, implications, and ethical considerations stemming from the groundbreaking discoveries in stem cell research. Stem cell research, as a beacon of light and hope within the medical and biotechnological domains, heralds the potential of stem cells in the treatment and recuperation of diseases. Nevertheless, this path is laden with intricate ethical, technical, and regulatory challenges, thereby necessitating precision and prudence in both its research and application.

E. Conclusion

In summary, stem cell research in Indonesia has advanced swiftly, with its discoveries being applied in the treatment of diverse ailments. The Indonesian government has enacted policies addressing numerous facets of stem cell science, including its production, application, and utilization, from both medical and religious perspectives. These regulations aim to ensure legal certainty, safety, and comfort for patients and stakeholders. However, the application of stem cells remains restricted and is primarily confined to research contexts.

Although the government acknowledges stem cell therapy as a healthcare initiative, it has not officially endorsed it as a standard treatment modality within Indonesia. Consequently, financing for stem cell therapy is currently provided through research grants or community contributions, without governmental support. There is a pressing need for the government to update its policies on stem cell therapy to reflect ongoing scientific progress and the evolving needs of society. Policy enhancement, aimed at fostering health technology use, could be achieved by investing in human resources, budgeting, and infrastructural development within the stem cell domain.

Stem cell therapy ought to be integrated into Indonesia's healthcare framework, enabling patients and the general populace to access stem cell treatments through the national health insurance scheme. It is anticipated that stem cell therapy will, in the foreseeable future, become an integral component of Indonesia's official healthcare services. This integration would ensure that all segments of Indonesian society in need of such treatments can access them safely and affordably. Furthermore, Indonesia could become a destination for global patients seeking stem cell therapy, thereby contributing significantly to the international medical community by elevating life quality and health standards.

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