

Stem Cells and Psyche: Perspectives and a Review of the Literature

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ABSTRACT In the 20th century, bone marrow transplantation evolved great expectations in the medical community and gained enormous popularity in society ever since. With the discovery of other stem cell sources, the designation of ‘bone marrow transplantation’ was replaced with ‘stem cell transplantation’ in clinical practice. The adaptation and response of patients, patient relatives, custodians, donors, and healthcare providers to current treatment approaches developed a serious psychosocial entity. Moreover, the psychosocial entity can be further complicated by various organic mental diseases, which may arise as a consequence of serious illnesses and burdensome treatments. An independent area of expertise is essential to evaluate, diagnose, and solve all these problems with a scientific approach. Correlating the organic and psychological components of the patient’s condition, facilitating communication between patients, doctors, families, and hospital systems, and counseling-liaison work have emerged as one of the most challenges of psychiatric skills. This necessitated the presence of a Consultation-Liaison Psychiatry (CLP) that undertakes this mission. First, basic principles and associated features of hematopoietic stem cell transplantation (HSCT) from the perspective of the clinician, patient relatives, and custodians, and expectations will be discussed. Afterward, the transplant unit from the viewpoint of the patient relatives and custodians and the perspective of child psychiatry and symptoms of burnout in an HSCT team will be discussed. Thereafter, the experiences and difficulties faced by the HSCT team in being a researcher and a student will be analyzed. Finally, ethical and legal issues pertaining to our country and the world will be discussed. We hope that this review will provide a scientific interpretation to the healthcare providers who experience the same difficulties in many different areas.

Keywords: Bone marrow transplantation; consultation-liaison psychiatry; hematopoietic stem cell transplantation

Although stem cells and psyche seem to be unfamiliar, they indicate an advanced healthcare approach. In the 20th century, bone marrow transplantation exhibited a high expectation in the medical community and had immense popularity in society ever since. In clinical practice, the designation of “bone marrow transplantation” has been replaced with “stem cell transplantation, when stem cell sources other than bone marrow were discovered. Within the past 30 years, Ankara University Stem

Cell Transplantation Unit executed around 3000 stem cell transplants.

A serious psychosocial entity has been generated with the adaptation and response of patients, relatives, donors, and healthcare providers to current treatment approaches. Furthermore, organic mental diseases may result from serious illnesses, and heavy treatments can further complicate the psychosocial entity. The need to evaluate, diagnose, and solve all these problems in a scientific manner reveals the pre-

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requisite of an independent area of expertise. Associating the organic and psychological components of the patient's condition, facilitating communication between patients, doctors, families, custodians, and hospital systems, and counseling-liaison work have emerged as one of the most challenges of psychiatric skills. For this reason, the presence of a Consultation-Liaison Psychiatry (CLP) that undertakes this mission is essential.

Since 1992, significant clinical support is provided by the Consultation Liaison Psychiatry to stem cell transplantations in Ankara University. This review will focus on the stem cell transplantation journey at Ankara University for nearly 30 years in the light of CLP.

Stem cell transplantation, being one of the most advanced treatment modalities in clinical practice, ignites high hopes for the cure in many patients. The expectations of these patients, the constraints they experience during the treatment, the unethical practices encountered by them, and the difficulties faced by the scientists who are eager to study and desire to work, cause a slightly different psychosocial situation. We believe that this is the very first platform in which all psychosocial issues are discussed on scientific grounds.

First, the basic principles and associated features of hematopoietic stem cell transplantation (HSCT) from the viewpoint of the clinician, patient relatives, and custodians, and expectations will be highlighted. Afterward, this review will also discuss the transplant unit from the eye of the patient relatives, from the perspective of child psychiatry and symptoms of burnout in an HSCT team. Soon after, the experiences and difficulties encountered by the HSCT teams in being a researcher and a student will be analyzed. Finally, ethical and legal issues in our country and the world will be considered. We anticipate this review will deliver a scientific view to the healthcare providers who experience the same hurdles in various diverse areas.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Stem cells, found in every organ, are the cardinal cells that possess the ability of self-renewal and dif-

ferentiation into mature progeny.¹ Stem cells can be referred to as adult (somatic) and embryonic stem cells. Stem cells can be either totipotent, pluripotent, multipotent, or unipotent. The multipotent cells which can differentiate into mature blood cells are designated as hematopoietic stem cells (HSC). HSCs play a vital role in the maintenance of the entire hematopoietic system.² HSC transplantation can be defined as the first therapeutic utilization of adult stem cells. HSC transplantation (HSCT) can be categorized as 'autologous' or 'allogeneic' hematopoietic stem cell transplantation.³ In 1957, Donnall Thomas reported the first allogeneic HSCT to a patient, whereby he was awarded the Nobel Prize in 1990.⁴ Afterward, in 1961, the first autologous HSCT was performed. In the subsequent years, not only for hematological diseases, but HSCT was also considered as a curative therapeutic option for immune deficiency syndromes. European Bone Marrow Transplantation (EBMT) Society was established in 1974. Over 500 centers from 65 countries are registered with the EBMT society.⁵ Ankara University School of Medicine Bone Marrow Transplantation Unit is also one of the EBMT centers. To date, 1126 allogeneic, 1043 autologous HSCTs, and 475 allogeneic HSCTs have been conducted in the adult BMT (Bone Marrow Transplantation) and pediatric BMT units, respectively.

The autologous HSCT aims to provide high dose treatment (chemo/radiotherapy) and treat the complications with patients' own stem cells. HSCs of the patients have to be collected from peripheral blood or bone marrow and cryopreserved after processing for purification and cryopreservation before autologous HSCT. During autologous HSCT, a patient initially receives a conditioning regimen (chemo/radiotherapy), and on the day of transplantation, the cryopreserved transplant product is thawed and transfused to the patient. The aplasia period is considered as the first post-transplantation period until the engraftment (an increase of neutrophils and platelets). During this phase, the patient experiences various side effects, including mucositis, nausea, vomiting, diarrhea, oral intake deficiency. Infections due to either bacterial, viral, or fungal organisms can be observed. Despite the recovery of the

blood counts, patients continue to be immune deficient up to three months. Autologous HSCT is a feasible preference for lymphoma, multiple myeloma, occasionally acute leukemia, germ cell tumors, and autoimmune diseases.^{6,7}

In the allogeneic HSCT setting, HSCs of a healthy donor are transfused to the patient without any cryopreservation. Similar to autologous HSCT, the patient receives a conditioning regimen, and the collected HSCs from a healthy donor are administered to the patient on the transplantation day. In the post-transplantation period, unlike autologous HSCT, additional immune-suppressive treatment is given to the patient to minimize the risk of graft rejection and the onset of the graft versus host disease (GVHD). Besides infections and other complications perceived in autologous HSCT, GVHD is the major complication observed in an allogeneic HSCT patient. Allogeneic HSCT exists to be the sole curative treatment for hematological malignancies such as acute, chronic leukemia, myelodysplastic syndromes, refractory lymphoma, and also for benign hematological diseases such as aplastic anemia and other bone marrow failures, sickle cell anemia, thalassemia, and some other congenital immune/metabolic diseases. In the case of allogeneic HSCT, human leukocyte antigen (HLA)-compatibility of the donor with the recipient is essential; however, blood group compatibility like solid organ grafts is not a requisite. An HLA full match sibling is the primary choice as a donor but can be available for only 25% of the patients. Unrelated donors prevail to be a valid option in one-third of the rest.

Matched donors are unavailable in about 40% of the patients, so alternative HSCT from haploidentical donors or cord blood may be feasible for these patients.⁸ According to the EBMT data, haploidentical transplantations had increased worldwide until 2016.

In conclusion, HSCT is a curative treatment procedure for numerous hematological and non-hematological diseases. During the transplantation period, either physical or psychosocial complications may be perceived among patients and also among physicians.

THE PATIENT IN THE EYE OF THE DOCTOR, PATIENT RELATIVES, CUSTODIANS, AND THEIR EXPECTATIONS

It would be better to start by mentioning; who is the doctor?

A doctor is a physician, a scientist, a person who offers alternative therapies, gives unconditional services, predicts the future, determines the problems, and finds the solutions. The patients often perceive doctors as individuals having extraordinary powers, coupled with the ability to predict the future. The most obvious manifestation of this is stem cell transplantations!

However, the insufficiency of stem cell transplantation in a few cases is also established. Therefore, it is necessary to unearth new solutions.

Extensive laboratory studies and clinical applications enable the doctors to offer accurate use of advanced therapy medicinal products (gene therapy medicinal products, somatic cell therapy medicinal products, tissue-engineered products, and advanced therapy medicinal products combined with a medical device as an integral part of the medicinal product).

IF WE EXPLORE THE STAGES OF SOMATIC CELL TRANSPLANTATION (SCT)

In the Period of Diagnosis and Treatment of the Disease

When does the disease first find someone? This commonly occurs when everything seems alright, during the period of retirement and to someone who is planning to spend time with their grandchildren, or after a great sadness, during pregnancy or just so unexpectedly.

At such a moment, the physician must convey the truth to the patient in the most appropriate language. Patients are eager to know but do not want to hear about the facts. During this period of adaptation to acceptance, various confusions crop up in a patient's mind. As a team, it is of utmost importance to support and guide the patient in this period. The moment when a soul cannot tell the stem cells, or vice versa, is exactly this process!

The Coordination Center of the SCT Unit Before the Stem Cell Transplantation

In this process, the pre-transplant preparation of the patients is accomplished. Information regarding the

transplantation process is communicated. Consent forms are taken. The patience and empathetic approach of the coordination staff is of great importance.

Stem Cell Transplantation Process in the Stem Cell Transplantation Unit

In this process, the patient encounters a new medical team. With the support of a custodian, the patient resides inside the unit for a minimum of 30 days, takes chemotherapy and radiotherapy, and may also suffer from various noxious effects such as insomnia, lack of appetite, mouth sores, weakness, bleeding, diarrhea, shortness of breath, etc. In the unit, 24-hour continuous healthcare support and care are provided to the patient. Both the patient and the custodian, who feel confined and tired, reveal the urge to return to their normal lives, as soon as possible.

The Early-Stage After SCT

The happiness of being at home in this period is indescribable! The most positive phase in the process of bone marrow transplantation includes meeting one's child and their spouse!

The patient is treated with various drugs (immunosuppressives, antibiotics, etc.) and lives in a wide variety of situations as an outpatient follow-up (various infections, blood transfusions, hospitalizations). Expectations are high in this period whereby the patient wants to recover immediately, exhausting his or her patience. The soul feels impatient and tired!

The Late Period After SCT (Two Years and After)

This is the phase when the patient says: "It's enough, I'm better!" The risks of infection of the patient and the number of medications used by the patients are reduced. The patient can now continue their lives by themselves and be grateful to their custodians and donors, and their life continues.

But the question, which can never be answered, is still there: Why me?

THE EXPERIENCES OF THE HSCT TREATMENT TEAM

In addition to the follow-up, prevention, and treatment of complications in the transplantation process,

physicians and nurses play significant roles in providing emotional care to the patients and their families. During transplantation, disease control or cure usually gain the primary focus of the patients, their families, and staff. Owing to the intensive working conditions, various levels of stress indulge among healthcare workers. To maintain an emotional distance from sympathetic relationships with patients and their relatives, healthcare workers have the chance to gain more empathy and vision with various psychosocial tactics.⁹ Nevertheless, emotional depletion may arise from constant pressure and exposure to the suffering of patients and their families. This may lead to a decrease in the willingness to work, loss of flexibility in patient care, tendency toward the termination of work, absence and delay at work, erroneous medical practice, disregarding the problems of patients, and damaging the environment of their workplace.¹⁰ The motivation of the team to deal with stress under heavy workload is of utmost importance to prevent such situations.

THE TRANSPLANT UNIT IN THE EYES OF THE PATIENTS FAMILY

The transplant unit has its own physical and emotional drawbacks for the patient. Patients bring the background of their primary diseases, associated with the risks in the transplantation process. In an isolated unit, patients have to spend their time in solitude, away from their relatives, encased with high-tech devices and very busy staff without time for interpersonal contact, all of which impart feelings of loneliness and thoughts about the meaning of life. Economic conditions or the future of themselves and loved ones may develop anxiety and stress in the patients.¹¹ Enhanced demands of social and physical support have some results, such as feelings of being a burden for loved ones and feeling the loss of control on the patient's own life. Depression, anxiety, and adjustment disorders are triggered as a result of all these issues. Regression is another outcome of an isolated environment; which is related to the immature behavior or pathological personality traits to become evident. The patient can end up being irrational and uncooperative with or even intimidating to the staff.

A family is waiting with hope and anxiety outside the transplant unit. According to the systems theory, there is a unique social system for each family. Each member of the family is bestowed with their roles, duties, and coalitions in the system.¹² A family has its borders and rules.¹³ The dissemination of roles and tasks remains unchanged until a crisis is encountered such as a diagnosis of a serious disease in a family member. Adaptation to this new situation is crucial for the family during the diagnosis and transplantation process. Family coherence increases, altering the role distribution.¹⁴ Some variables of the family are responsible for this adaptation process. Each family has its perception regarding the outside world and the hospital. They accompany all these beliefs to the transplant unit. Guilt develops in case they feel a connection between the patient's disease and themselves. In Turkish, there are various idioms like; "to dry someone's bone and marrow" or "make someone cancer". It is impossible for the family members not to reflect their guilt on the staff, which invites allegation about malpractice or trying experiments on their patients. Some family members are open to the staff, while others are more distant. The families' levels of development, belief systems, structure, and the affection of the relatives for the patient are responsible for these attitudes. Sometimes family members are disconnected, and it is the responsibility of the staff to inform everyone. Conflict within families may also be reflected in the hospital.

All family members need hope, and they are eager to receive up-to-date information about their patients' medical status and prognosis. However, for a better understanding of the patients' relatives, use of medical terms should be avoided. They may be provided more information than they need. Nonetheless, it is better to give the relevant information they can cope with. The best way to achieve this is to ask the relatives their opinion about the status of their patients.

Nowadays, relatives more often discuss internet information with the staff. The staff has to explain that every information available on the internet may not be true or may not reflect their patients' unique situation.

FROM THE PERSPECTIVE OF CHILD PSYCHIATRY: HSCT AND CHILD MENTAL HEALTH

HSCT is increasingly finding its application in the treatment of various both hematological and non-hematological, malignant and nonmalignant diseases in childhood and adolescence. Diagnosis and treatment of cancer that includes HSCT particularly, during childhood or adolescence, may interfere with the developmental processes, such as physical, psychological, cognitive, emotional, and social development. HSCT treatment indulges in less opportunity for independence, school attendance, and social maturation.¹⁵

Recent research has enlightened that high risk of short-term and long-term psychiatric disorders are associated with HSCT survivors. Studies reported that 80% of children suffer from mild psychiatric problems. Significant increases in anxiety, depression, and aggression are experienced by 40% of children, in the months following the transplantation. The high prevalence of the major depressive disorder, generalized anxiety disorder, and post-traumatic stress disorder (PTSD) among the specific population of pediatric HSCT survivors have been documented. Several studies reported that during the six months post-HSCT, depression, peer isolation, and behavior problems are frequently experienced by a consistent number of patients. Pediatric BMT survivors also exhibit a decreased quality of life, increased rates of behavioral disorders, impaired neurocognitive abilities, and a decline in social competence and self-concept. The severity of symptoms enhances with prolongation of hospital stays and transplantation at a younger age.^{15,16}

With a consistent and alarming increase in the number of long-term survivors of childhood cancer and HSCT, an extension of psychosocial care to this population is suggested by the researchers. Thus, a more specific, well-coordinated multidisciplinary care system is essential for HSCT survivors.

BURNOUT AMONG HSCT STAFF

A cluster of symptoms associated with chronic stress involving domains of emotional exhaustion, depersonalization, and reduced individual accomplishment is defined as burn-out.¹⁷ Burn-out is a work-related,

multidimensional syndrome.¹⁸ Well established risk factors for burnout includes excessive workload, an imbalance between job demands and skills, dearth of job control, and prolonged work stress.¹⁹ Since the signs and symptoms of burnout are predominantly related to the workplace, it is not classified as a psychiatric disorder. However, in the absence of proper intervention, burnout may potentially progress toward psychiatric disorders.^{20,21} Investigations reveal that occupational stress has been reported as an important issue in the case of physician burn-out.²² Owing to difficulties in their jobs, healthcare professionals are prone to the unfavorable consequences of occupational stress and stress-related problems. Nearly fifty percent of the physicians are reported to be at burnout condition.²³ Although there are some differences across studies, physicians associated with specialties such as emergency medicine and family medicine are at greatest risk for burn-out.²⁴ Among all physicians, the rates of burnout for pediatric medical oncologists/hematologists rank in the middle.²⁵ Similar rates have been registered for HSCT professionals. Neumann et al. reported burnout rates of 38% for nurses, 41% for physicians, 53% for pharmacists, 30% for social workers among HSCT professionals. The development of burnout conditions among the HSCT professionals may be attributed to their high workload and the management of care for this complicated clinical population.²⁶ However, it is quite rational that the impact of this stress on all employees is not the same. The support of the team, professional satisfaction, and regulation of the working hours may

potentially improve coping. The stress and related burnout condition can be recovered with appropriate support mechanisms and humanistic approaches. Long-term untreated burnout may result in health problems and also reduce the quality of care, professional satisfaction, and accomplishment.²⁷ Most of the studies conclude that the consequences of physicians' burnout lead to increased risk of medical errors, reduced quality of patient care, resulting in lower patient satisfaction.^{18,27} Because of all these associations, physician's distress is thus considered to be an important quality indicator for hospitals.²⁸ Individual and organizational level strategies are recommended to cope with a burnout in physicians. For example, Shanafelt and Roseworthy suggested several organizational strategies to reduce physician burnout. On the other hand, individual interventions typically involve psycho-therapeutic techniques, advanced communication skills, and personal coping strategies.²⁸ As a result, in our opinion, work-related stress among HSCT professionals is an important issue; it should be screened routinely by the organizations and intervened whenever required.

BEING A STEM CELL RESEARCHER AND A STEM CELL STUDENT

The philosophy of stem cell biology centers around three basic aspects. One aspect is the natural structure of the stem cells. The origin of stem cells is undifferentiated with self-renewable properties. However, it may differentiate into specialized cells that make up the organism (Figure 1).

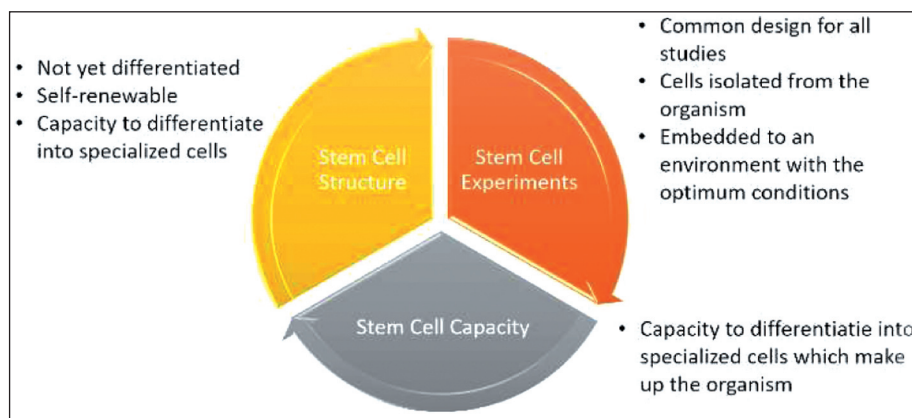


FIGURE 1: The steering wheel and the unconditional intersection of all aspects linked to stem cells.

Another aspect constitutes stem cell experiments. The first target of isolation of stem cells from organisms is the common design that is followed by all stem cell studies. A third aspect reflects the differentiation capacity of stem cells, which can make up for the whole organism.²⁹ The philosophy of stem cell biology motivates all researchers and students, making this area a burning topic of research in the field of biology.

Stem cell research initiated with the isolation of stem cells from cord blood for the first time and peaked with the discovery of induced pluripotent stem cells (iPSCs).³⁰ Consequently, John Gurdon and Shinya Yamanaka were awarded the Nobel Prize.^{31,32} Throughout the world, the attention of researchers was attracted by these developments and the nature of stem cells. Hence, various studies involving research on stem cells have been documented in the literature. More than two-fold increase was evident in the rate of research publications from 2008 to 2012.³³ Stem cell research explores multidisciplinary areas, including regenerative medicine, tissue engineering, and cancer. Many young researchers are enthusiastic about joining stem cell research with multidisciplinary aspects and shaping their career in this domain. Therefore, numerous graduates, PhDs, and post-docs from a variety of scientific disciplines are found to collaborate in this intriguing field of interest.

Almost half of all stem cell publications are associated with regenerative medicine or cellular therapy medicinal product development.³³ It is important to catch up with this pace of stem cells. Availability of trained researchers such as post-docs, funding programs, research institutes with cutting edge-infrastructure contribute to the major factors influencing stem cell research. Each of these has a different impact on researchers and their psychological mode while pursuing research activities. A sense of responsibility is comprehended by the researchers during stem cell research. The knowledge of the incredible process of transformation of a single cell into the whole organism is exciting for the researchers. Along with this excitement, the researchers' responsibilities and ethical concerns are augmented. At this point, stem cells touch our souls (Figure 2)!

The fundamental pillars of regenerative and restorative medicine involve novel cellular and tissue-based products intended for human application and biotechnologically manufactured human medicinal products. The raw material of such products is generally donated human tissues or cells (Figure 3). In the case of human donation, moral values and ethical norms have to be adapted one-to-one in the light of the cultural and geographical position of a country or region.

Cellular therapies have already reserved a spot, as far as drug discovery is concerned. In certain medical indications, cellular therapies can even promise, today, clinical superiority. Even though early clinical evidence proves positive results, there are a limited number of authorized cellular therapies yet.³⁴ A number of reasons contribute for the time-consuming process of development of cellular therapies, of which the most substantial part is reserved for the way cells act during the isolation processes, along with obstacles in providing research material in a timely and affordable manner, and hurdles pertaining to clinical trials, regulatory frameworks, and infrastructure. When scientists start working with cellular content, they are uncertain about the cells' activity while being isolated and proliferated. Maintaining the cells steady during expansion is a major challenge. By product formation and differentiation, dedifferentiation, chimerical structure formation need to be closely monitored for any risky outcome. Translation of stem cell research to clinical applications is thus difficult owing to such factors. It is also somewhat

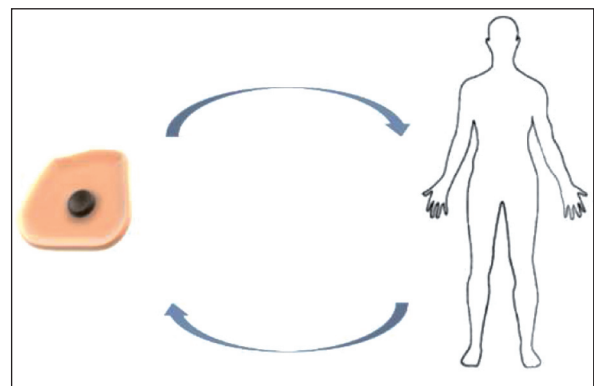


FIGURE 2: Human-based stem cells constitute the whole organism, which treasures the same cells to be provided for use in human-based cell and tissue research. This is the reason why stem cell research is directly linked to our souls.

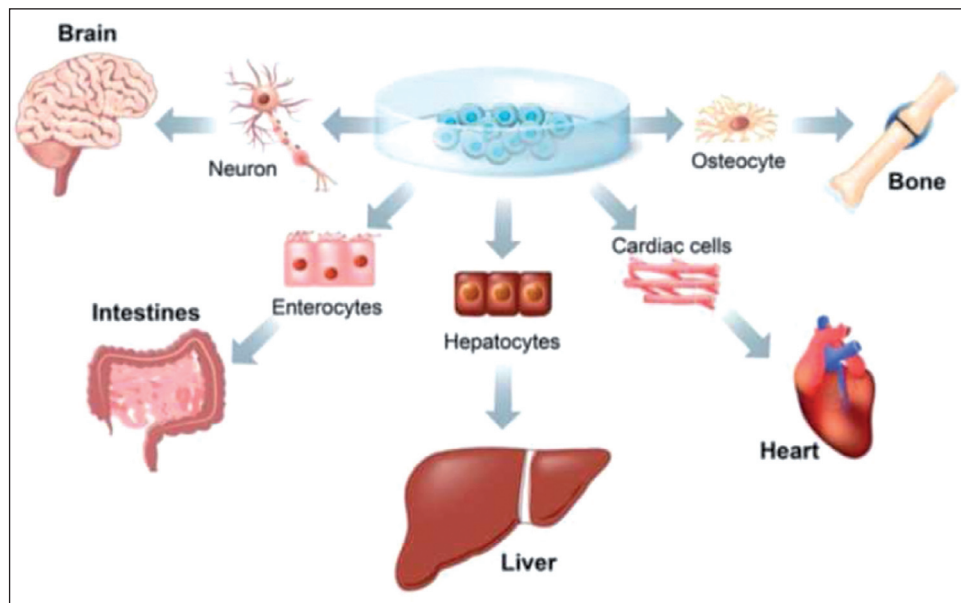


FIGURE 3: Cells sources as starting materials of biotechnologically manufactured human medicinal products.

difficult to meet regulatory stipulations. To be able to go through all such procedures without bottlenecks is yet a utopia. Finding the appropriate and sufficient financial support often creates hindrance in the way of proceeding with research on stem cells.

Scientists experience several hurdles in the course of stem cell research. The first and most vital is financial insufficiency. Stem cell research is about ten times more expensive than other studies; therefore, exorbitant financial support is inevitable to continue with such studies. Recruitment of expert staff and an experienced research team for these studies also incur strong financial support. The lack of infrastructure of the research centers is the second constraint. Many researchers complain about incomplete and inadequate research centers. Insufficient equipment restrains the researchers from accomplishing their research. The third difficulty is the waiting period. Research materials used during stem cell studies have to be imported by many countries. These import activities of companies indulge in long latent periods that have to be faced by scientists. Therefore, it becomes difficult to complete theses, projects, and articles that need to be published during such a waiting period. Due to the difficulties summarized above, many young researchers are unable to finish their research lifecycles within their scheduled timeframe.

Tem Ham et al. have recently reported their questionnaire results based on the challenges faced during research and development of cellular therapies.³⁵ Accordingly, most of the challenges are experienced with regulatory hurdles in the European Union. Researchers are mostly unaware of the necessities stipulated by governmental organizations, nor is it vice versa. Next comes the technical challenges mostly faced due to difficulties in obtaining specific quality standards and maintaining a continuous supply chain. Knowledge gaps may arise in the course of research. Such gaps can be fulfilled by recruiting and training experts, which, in turn, requires good human resource management and adequate funding. Confronting all these limitations, it is still challenging to establish the efficacy and safety of the cells in question. The vicious circle, therefore, continues, both for the researchers and their following students.³⁵

THE ETHICAL, LEGAL AND REGULATORY STANDPOINT OF REGENERATIVE AND RESTORATIVE MEDICINE RESEARCH AND APPLICATIONS

So what is ethics, literally? Ethics originates from morality. Morality is the determination of what is right and wrong and doing what is right. Ethics, hence, can be defined as the act of moral values.

The ethical approach is, therefore, the reflection of moral values on doing it right no matter what the circumstances. The core of human donation and transplantation ethics can be regarded as altruism. The term altruism is derived from the French word “autrui”, which means “another individual”. The terminology was first coined by the French author and philosopher, Isidore Auguste Marie François Xavier Comte (1798-1857), the father of positivism.³⁶ In the altruistic approach, disregarding the consequences on themselves, the individuals focus on the consequences of their actions on others. This can also be explained by self-sacrifice and devotion.

REGIONAL VARIATIONS TO THE APPROACH OF HUMAN TISSUE AND CELL DONATION

In the case of human donation, certain consents from both the donors and recipients are mandatory these days. In some countries, the donation is performed with expressed consent (e.g., the US, Canada, Denmark, Brasil), whereas in others, with presumed consent (e.g., Spain, Belgium, Austria, France, Norway, Italy, Singapore). Expressed consent necessitates the donors to claim the donation on any of their legal certificates or via any of their legal guardians. Conversely, presumed consent involves potential donors by birth who have not explicitly claimed otherwise (direct objection sent to competent authorities, third party claim expressing the objection of the potential donor, etc.).³⁷ Along with their recipient patients, responsible physicians and other healthcare professionals are also obliged to sign a written informed consent. In order to track and trace the lifecycle of a donated tissue or cell until it reaches the recipient, implementation of a well-established national or international monitoring system is the need of the hour.

All countries or regions do not adhere to the same donor eligibility criteria. Rules tend to vary from one culture/ethnicity to the other. For instance, the United States of America (the US) is not so rigid when it comes to HTLV (Human T-cell Lymphotropic Virus) I/II, CMV (Cytomegalovirus), EBV (Epstein-Barr Virus) testing. In this case, the funda-

mental goal is to detect if the tissue is free of rich viable leukocyte content. In case it is present in the donated tissues or cells, such testing is mandatory.³⁸ On the other hand, the European Union (EU), substantially stipulates such testing regardless of the rich viable leukocyte content of the donated tissues or cells.³⁹ Another example can be cited from Canada. Canada does not accept individuals for blood donation if they have resided in Saudi Arabia between 1980 and 1996. This is because Canada recognizes that there was a large volume of meat trade from the United Kingdom (UK) to Saudi Arabia for six months or more within those years, thereby, leading to the risk of vCJD (variant Creutzfeldt-Jakob Disease) transmission.⁴⁰ On the contrary, Turkey does not consider it as a drawback for a donor to have lived in Saudi Arabia within the course of the said term. In Turkey, minimal testing criteria for all donors are anti-HIV1,2 (Human Immunodeficiency Virus) for HIV1 and HIV2, HBsAg and anti-HBc for Hepatitis B, HCV antibody for Hepatitis and syphilis. Further, HTLV-1 antibody testing is executed on those individuals who have resided in territories with a high prevalence of HTLV-1-related diseases, individuals who personally or whose parents have ethnic roots from such territories or those who have sexual partners coming from such territories. In cases where anti-HBc is positive, and HBsAg is negative, further testing is mandatory to evaluate the risk for clinical eligibility of such patients. Furthermore, an approved testing algorithm is performed in order to rule out the presence of active *Treponema pallidum* infection. Regardless of the specificity of a testing method, negative results may be sufficient within the release criteria. However, the positive *Treponema* result obtained by the use of a non-specific testing method can be rejected if the specific test method yields negative results. When *Treponema*-specific test results are positive, detailed risk assessment of the donor is a prerequisite for evaluation of clinical eligibility. In some special circumstances, RhD, HLA (Human Leukocyte Antigen), malaria, *Toxoplasma*, EBV, *Trypanosoma cruzi*, and additional tests may be employed based on the medical history of the donor or the characteristics of the donated tissues or cells themselves.⁴¹

ETHICS IN CELLULAR THERAPY RESEARCH AND DEVELOPMENT

Altruism and ethics are the foundation of human donation and transplantation. However, tissue/cell banking that is essential for regulating the safety and quality of human tissues and cells has brought up recent trends such as merchandising. Merchandising is associated with the risk of jeopardizing altruism and ethics. A dearth of regulatory control can accumulate the risks to damage moral values. Such risks can be listed under three main categories: i) donation, ii) tissue/cell banking, and iii) transplantation.

Risks in a donation:

- Financial incentives
- Storage for future use
- Use without consent
- Unauthorized archiving and extended use

Risks in tissue/cell banking:

and cells

- Purchasing in order to access human tissues
- Priorities related to donation
- Quality reflected onto pricing
- Directed manufacture
- Financing/profit margins
- Conflict of interest

Risks in transplantation:

- Sales discounts
- Manipulated costs
- Directed sales and marketing
- Biovigilance gaps
- Costs exceeding fees
- Incentives related to indications for use/therapeutic area

Therefore, regulations are inevitable. The primary objective of regulations is the protection of public health. The aim is, therefore, to make conformity assessments, grant licenses, and take a record of activities. Quality and safety data, along with controlled trade activities, are substantially included in the as-

essment criteria for conformity. Conformity assessment is executed throughout the lifecycle of human donation and transplantation. The lifecycle initiates with fostering donation and continues with a donation, tissue/cell recovery, manufacturing and process validation, product specifications and release, distribution, ending with transplantation, storage, or research. Tools that are useful in conformity assessment include adverse event/effect reporting, clinical monitoring, regulatory tracking, traceability, periodic regulatory controls and inspections, and biovigilance.

The central laws implemented by the competent health authority of a given country or region are followed to conduct the conformity assessment. Some competent authorities for human tissues and cells are listed below:

Turkey: Turkish Ministry of Health Directorate-General of Healthcare Services (SHGM) [T.C. Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü]

Turkish Medicines and Medical Devices Agency (TİTCK) (Turkish Medicines and Medical Devices Agency)

UK: Human Tissue Authority (HTA) (Human Tissue Authority)

Finland: Finnish Medicines Agency (FIMEA) (Finnish Medicines Agency)

France: Ministry of Health, National Agency for Security of Medicines and Healthcare Products (ANSM) [Agence nationale de sécurité du médicament et des produits de santé], Biomedicines Agency (ABM) [Agence de la biomédecine]

Germany: German Federal Ministry of Health (Federal Ministry of Health (Germany)), Paul-Ehrlich-Institut (PEI) (Paul-Ehrlich-Institut)

The Netherlands: Ministry of Health, Welfare and Sport (Government of the Netherlands. Ministry of Health, Welfare and Sport), Health and Youth Care Inspectorate (IGJ) (Health and Youth Care Inspectorate)

Spain: National Transplant Organization (ONT) [Organizacion Nacional de Transplantes]

The full list of competent authorities for tissues and cells in the EU can be obtained at the European Commission website.⁴²

TURKISH LAWS AND REGULATIONS IN THE FIELD OF STEM CELLS

In Turkey, regulatory activities are shared between the two bodies of the Turkish Ministry of Health. The Directorate-General of Healthcare Services (SHGM) is responsible for organ and tissue transplantation, healthcare services, conventional tissue products, stem cell clinical trials, the Turkish Organ and Tissue Information System (TODS), and the Turkish Stem Cell Coordination Center (TÜRKÖK).⁴³ Turkish Medicines and Medical Devices Agency (TİTCK) is accountable for human medicinal products, medical devices, advanced therapy medicinal products, biological and biotechnological products.⁴⁴ Differences are also observed in the legislative documentation governed by these two bodies.

SHGM:

- Provisions 90 and 91 of the Turkish Punishment Law⁴⁵
- National Law on Organ and Tissue Procurement, Storage, Transfusion, and Transplantation⁴⁶
- National Directive on Organ and Tissue Transplantation Services⁴⁷
- National Directive on Human Tissues and Cells and the Quality and Safety of Related Centers⁴⁸
- Public Announcement related to Embryonic Stem Cell Research (2005/141)⁴⁹
- Public Announcement related to Non-Embryonic Stem Cell Studies Intended for Clinical Application (2006/51)⁵⁰
- Guideline on Non-embryonic Stem Cells Intended for Clinical Application⁵⁰
- Public Announcement related to Stem Cell Studies (2018/10)⁵¹
- Guideline on Tissue and Cell Clinical Trials and Clinical Attempts⁵¹

TİTCK:

- Regulation on Clinical Trials of Medicines and Biological Products⁵²
- Regulation on Manufacturing Plants of Medicinal Product for Human Use⁵³

- National Announcement on the Licensing of Human-based Tissue and Cell Products and Related Centers⁴⁸

- Regulation on the Registration of Medicinal Products for Human Use⁵⁴

- Draft Guideline on Advanced Therapy Medicinal Products⁵⁵

Primarily involved in organ and tissue procurement, the SHGM is also applicable for topics related to bone marrow procurement and transplant when it comes to governing tissues and cells.⁴³ This is administered by the Department of Organ, Tissue Transplantation and Dialysis Services (<https://organ.saglik.gov.tr/Index.aspx#>). The above-mentioned Department takes its decisions with the opinion of its scientific commissions wherever necessary. On the other hand, inspections/audits, licensing of manufacturers, and registration of products such as medicines, medical devices, and cosmetics are supervised by the TİTCK (Turkish Medicines and Medical Devices Agency). The TİTCK also hosts the central ethics committee and takes its decisions consulting with its scientific commissions whenever necessary.

STEM CELL CLINICAL TRIALS IN TURKEY

Recently in Turkey, clinical applications of cellular therapies are classified as standard therapies and experimental studies. To date, hematopoietic stem cells are the only standard therapies defined in Turkey. Accordingly, experimental studies cannot be applied to patients as a treatment option. Clear instructions are also provided in the legislation prohibiting the advertisement or promotion of experimental studies in the press unless the studies are concluded, and approval from the Turkish Ministry of Health is achieved. It is forbidden to mislead the public via television, daily journals, or social media with any kind of information promising hope with a lack of scientific data. Experimental studies are also categorized into two sub-groups: clinical attempts and clinical trials. Clinical attempts are established on the 90th provision of the Turkish Punishment Law.^{45,51} Here, clinical attempts are broadly defined as a consented attempt with the aim to treat humans on the grounds that current common medical inter-

ventions will fail to yield any outcome. However, clinical trials are a little different. As is known commonly, clinical trials are research investigations whereby people volunteer to verify new treatments, interventions, or tests with the aim to prevent, detect, treat, or manage various diseases or medical conditions. In Turkey, there is a limitation in the number of patients enrolled for clinical attempts. For the same intended clinical indication, a physician can apply for clinical attempts of a maximum of three patients. He/she then has to continue with a clinical trial application.⁵¹

REGULATORY HURDLES AND REFLECTIONS ON TURKEY

Legal regulations in Turkey bestow a number of hurdles. It may be useful to analyze at least a few of these. In the US and EU, cellular and tissue-based products are primarily classified as minimally manipulated and substantially manipulated. FDA (Food and Drug Association) has defined minimal manipulation as processing that does not modify the original relevant characteristics of the structural tissue relating to the tissue's utility for reconstruction, repair, or replacement and processing by which the relevant biological characteristics of cells or nonstructural tissues remain unaltered.⁵⁶ EMA (European Medicines Agency), on the other hand, has defined non-substantial manipulation as cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.⁵⁷ However, in Turkey, the terminology minimal or non-substantial manipulation has not yet been defined in the classification of tissue and cellular therapies. Nonetheless, according to the Draft Guideline on Advanced Therapy Medicinal Products, prepared on the basis of the EU Directive 1394/2007 and recently submitted to public consultation, substantial modifications are expressed as any process excluding cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.⁵⁵

Although the definition seems to be arriving soon, it is still not known how and by whom such products with non-substantial manipulation will be regulated. The procedure and application of the intended treatment with cellular and tissue-based products still leave a question mark in application holders' minds. The US and the EU regard all cellular and tissue-based products, either minimally or substantially manipulated, as "medicinal healthcare products intended for human application". No discrepancy is observed between minimally or substantially manipulated products, and both categories are well-regulated within the body of assigned competent authorities. Which cellular and tissue-based interventions need to be considered as products and which others as therapies- remains a controversial issue in Turkey. It is extremely ambiguous for the physicians to decide as to under which legislative practice they should apply to authorities for approval. This also invites controversy to the reimbursement rules. It is still a hurdle for authorities to determine as to which of these shall be considered as medicinal products and which as healthcare treatment packages. Hence, the Turkish reimbursement schemes might exclude some therapies, having a world classification as standard therapy.

Turkey's national strategies for public health prioritize research and development of biotechnological products. Until recently, biotechnological products were substantially considered as human medicinal products of high-molecular-weight hormones, antibodies, vaccines, blood factors, growth factors, and biosimilar human medicinal products of such and cellular and tissue-based therapies were regarded as an infinitesimal portion of the said national strategies.⁵⁸⁻⁶⁰ In general, biotechnological products can be defined as biotechnologically developed and manufactured biological substances that structurally and actively resemble naturally existing substances in humans. Undoubtedly, cellular and tissue-based products are in line with this definition. Therefore, lately, with the acknowledgment of the case, research and development of such products have been incorporated within national strategies related to biotechnological products. In 2018, for instance, the Scientific and Technological Research Council of

Turkey (TÜBİTAK) approved the Regenerative and Restorative Medicine R&D Strategy Document of Ankara University Stem Cell Institute as one of the national strategy documents specifically related to research and development of cellular and tissue-based products.⁶¹

Brain drain is another bottleneck with legal regulations in Turkey. Brain drain does not necessarily happen with scientists relocating to other countries. It also happens when technical personnel resigns from their current job position to practice another duty. When personnel is lost, knowledge and expertise fade away. Reclamation of the infrastructure is time-consuming. Establishment of validated intercommunication systems that will restore the knowledge and expertise for the new coming personnel can, therefore, evade such circumstances. Brain drain also occurs when a governmental entity that has years of expertise starts sharing its mandate with another governmental entity that is new in the business. In this case, it takes time to realize who is actually in charge of which subject, where to apply to, how to apply, etc. Owing to brain drain, authorities are unable to timely issue recent developments to the public through their websites. As an example, as explained above, TİTCK is authorized for issuing manufacturing licenses.⁵³ Recently, the number of manufacturing sites approved for cellular and tissue-based products and the products approved for manufacture are not known for certain. One of the major challenges faced by the physicians and the public is that the difficulty in analyzing where to get cellular and tissue-based product manufacturing services.

Legislation regarding such products is still under development in Turkey. With passing days, constant improvement is witnessed. As some countries are pioneering research and development in cellular and tissue-based products, they are also introducing novel approaches to laws and regulations. Subsequently, international legislation evolves. Hence intensive harmonization practices are required to promote Turkish laws to international standards, which does not always happen on a timely basis. Therefore, gaps, present in the national legislation, unfortunately, indulge in various miscon-

ducts. First, gaps may-time to time-lead to delayed applications and assessments, resulting in delayed access of patients to their treatment. Once accessed, there may be severe mortality and morbidity issues that cannot be elucidated due to the dearth of biovigilance practices. This may lead to poor causality assessment associated with possible side effects and adverse events-the two issues crucial for public health concerns. Another drawback includes incomplete licensing application lifecycles of cellular and tissue-based products. Conventional medicinal products for human use endure a well-established legislative adventure, typically starting with the manufacture, continuing with clinical trials, and resulting in a proper marketing authorization application. Cellular and tissue-based products are not so lucky yet. Defined legislation is established for manufacturing licenses of such products. Moreover, clinical trial legislation also exists that is governed by both SHGM and TİTCK. However, even in the presence of legislation for marketing authorization applications, there was no obligation to apply for marketing authorization. With the upcoming Draft Guideline, rules are anticipated to be addressed by the most effective means possible. This will eventually ensure the reservation of a spot by the cellular and tissue-based products in Turkey under biotechnologically manufactured human medicinal products.

Penal sanctions for the commercialization, promotion, and advertisement of cellular and tissue-based therapies in Turkey have yet to be established. As sanctions are not clearly defined, rumors can critically mislead the public. The public is eager to invest thousands or millions of Turkish Liras in stem cell interventions with the hope of relieving their pathologies, ignorant of the consequences they may have to experience in the future. Recently in Turkey, we hear and read the news that reports success of stem cell injections to treat knee pain, that stem cell reunites patients with healthy lungs, thereby increasing their chance of survival, that a used-up heart muscle could be restored successfully with stem cell injection and that stem cell treatment could also restore the life of a patient with used-up brain cells.⁶²⁻⁶⁴ We also frequently witness beauty parlors administering subcutaneous stem cells

with the intent of skin rejuvenation.⁶⁵ We may come across such press releases that lack scientific evidence targeting patient populations in need, especially in stem cell interventions, which may, in the future, be of great disappointment to the public. The only way to avoid such a disaster is to implement proper laws based on accurate stem cell science and to illustrate the scientific outcomes to the public in the light of moral rules and ethical approach.

The rapid increase in stem cell research has made way to a part of therapies entering into the clinical phases. Hence stem cell therapies are gradually getting hold of patients in need. With the evolution of stem cell research, the development of a centralized regulatory framework to address the specific challenges related to cellular therapies is of utmost importance. Meanwhile, researchers can freely continue to enlighten the true nature and the safety and efficacy limits of cellular therapies.

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