SAMPLE OF RESEARCH REPORT

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INTEGRATION OF MAQASID AL SHARIAH AS A RECIPROCAL FRAMEWORK IN STEM CELL DERIVED ORGAN SYNTHESIS

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Abstract

The advent of stem cells has leveraged regenerative medicines and tissue engineering owing to its capability to differentiate from different somatic origins. This has opened the possibilities to create new organs and improved quality of life. In the current study, it was proposed that the utilization of stem cells can be manipulated to serve as a mean of transplantation alternatives and repairing lost tissues or organs. However, issues regarding the safety and efficacy should be the main focus in order to protect human dignity, lineage or inheritance and avoiding genetic manipulation for unnecessary means. This study aims to integrate Maqasid al-Shari'ah perspectives, highlighting associated bioethical principles in synthesizing new organs from stem cells. The study has consolidated textual analysis of the Qur'ān, Hadith, the works of Muslim scholars, particularly the works of theologians, scholars of Islamic law (fuqaha), and jurists (usul al-fuqaha) to describe and analyse the Islamic moral teaching and judgment on medical approaches.

Keywords

Organ, Maqasid al-Shari'ah, stem cells, 3D bioprinting, bioethics

INTRODUCTION

A large number of clinical trials have been conducted to cure for human ailments as number of cases keep increasing each year. As the number of human ailments continued to rise each year, a huge number of clinical studies have been conducted to find a solution. The use of pharmacological agents for therapeutic purposes have gained significant concern regarding its adverse events and non-specific drug interactions thereby limiting its use. Over previous two decades, stem cells have been shown to treat a wide range of diseases and could be a powerful tool for understanding human biology and development.

Stem cells refer to a highly proliferative cells that are capable to self-renew and differentiate into specialised cells. Based on the differentiation potential, stem cells can be divided into four groups; totipotent (can form all cell types of the body, includes placental or extraembryonic cells), pluripotent (can generate all types of tissues and organs, i.e embryonic and induced pluripotent stem cells), multipotent (form most cell types but with limited capacity, include cord blood or adult stem cells). In this study, we will focus on the pluripotent stem cells (PSCs) due to its robust functional characteristics.

In clinics, injuries or cell damage can be possibly treated using stem cell-based therapy originated from a specialised or differentiated cells. These fully mature cells can be used to replace damaged cells such as neuronal damage (Alzheimer's or Parkinson's disease), produces β-cells of pancreas that can secrete insulin oro generate skeletal myoblast to induce cardiac regeneration (Muller et al., 2018). In the case of tissues and organs that are completely destroyed or damage, generation or synthesis of a completely new whole organ would be an ideal choice. With the advent of stem cell technology, cells can be isolated, expanded and differentiated into various types of desired organs.

BACKGROUND

Development of the metanephric kidney depend on crosstalk between four progenitor cell populations (ureteric bud, nephron, stromal, and endothelial progenitors) in the nephrogenic zone. Advancement of human-PSC-derived kidney organoids has opened new avenues of research on kidney development and diseases. Also, the kidney organoids provide a three-dimensional (3D) in vitro model for the study of cell-cell communications in the developing kidney. Formation of higher-order, vascularized and functional kidney undoubtedly challenging. The current proposal aims to focus on major transcription factors and signaling cues that facilitate cell fate determination in native kidney. We will examine how an in-deep knowledge of cellular and molecular mechanism of kidney development can be translated into the dish, allowing the generation of 3D PSC-derived kidney organoids.

There are high demand for suitable kidney intended for transplantation. However, shortage of donors has left patients untreated and contributed to high mortality rate with respect to kidney failure. Thus, making a new kidney could be the solution. For this purpose, the new kidney can be used as a tool to understand the mechanistic action and signaling pathways of developing kidney, modelling kidney diseases that rise due to genetic modifications and provide functional kidney that can filter blood thus accelerating regenerative medicine therapies. If this can be translated into reality, millions of persons worldwide whose lives depend on a functioning kidney transplant or long-term dialysis, as well as those with end-stage renal disease can now be treated. The study aims to highlight the possibilities of creating healthy and functioning human kidney in-a-dish thus can be as a guideline to model acquired or congenital kidney diseases.

PROBLEM STATEMENT

Chronic kidney disease (CKD) affects 11–13% of the global population. The high prevalence of CKD in the elderly reported due to ageing and cardiovascular risk factors, whereas pediatric tumors (e.g., Wilms tumor) and congenital anomalies of the kidneys and urinary tract (CAKUT) are the most common cases in youngsters. As a consequence, two million people currently depend on dialysis with limited access to donor for kidney transplantation. The dialysis has affected the patients especially the lower socioeconomic status and limited alternatives. The regenerative medicine field can provide alternatives by forming kidney organoids derived from human pluripotent stem cells (hPSCs). Generation of hPSCs from healthy donors or diseased patients promoted personalised medicine for treatments of kidney diseases. Undoubtedly, generation of hPSC-derived kidney organoids offer innovative solution to create functional nephrons for patients with kidney diseases although experimental challenges remains to be addressed.

Patients suffering from kidney failure often opted transplantation as treatment of choice owing to increased longevity as compared to hemodialysis. Transplantation offers improved quality of life and is cost-saving for patients with end-stage kidney disease. In theory, this will reduce the expenditures accessing medical healthcare. However, the limited number of donor and time-consuming procedures for waiting suitable organs reduces the chance of recovery. This will severely affecting people of lower social status opting for any therapies. Consequently, there could be a direct purchasing of living kidneys that can be bought and sell uncontrollably. This commodification is opposed by health ethicists and Islamic authorities thus require establishment of new medico-legal policies. Also, with the advent of stem cell technologies, it is possible to generate healthy personalised kidney from patient cells. These autologous tissues will reduce chances of immunorejections and associated cinical manifestations. Recently, these cells have shown to mimic native kidneys in term of morphology and molecular functions. Although the realism of making new human kidney is near and there would be a rapid generation of futuristic ‘kidneys-on-demand’ in the market, ethical and Islamic guidelines must be outlined to predict the impact on socioeconomic, health, laws and policies thus providing essential information for Muslim countries and communities.

SCOPE OF THE STUDY

Practically, the study will cover wider issues and will benefit current Islamic institutions in making decisions relating to stem cells, transplantation from cells of their own (autologous), reversing the state of pluripotency, organ-donor issues, purchasing organs in the market, cell-of-origin issues (nasab), genome editing, utilisation of human embryonic stem cells and somatic cell nuclear transfer (SCNT). The study will provide religious awareness via virtual and physical platforms, promote healthy lifestyle, stem cell-derived disease prevention and clear up misinterpretations, misconceptions and misinformation regarding this technology. Ideally, the technical data will be shared and discussed among religious investigators to extrapolate, derive, interpret and summarise the findings in accordance with Islamic teachings, the Quran and hadith. The study will compile all technical discoveries in set of publications so that it would help Islamic institutions in drafting communication strategies or guideline for the benefits of societies.

OBJECTIVES OF THE STUDY

Integrating Maqasid Shari'ah in stem cell-derived organ synthesis:

1. To outline the quranic, Prophetic narrations and scholar views on creation of new organs and the implications on societies and policies.
2. To generate set of questionnaires to investigate knowledge, attitude and perceptions on stem cells utilization in medical settings
3. To update the current religious opinions regarding hiPSCs and genome editing
4. To create awareness on the permitted and prohibited manipulation of stem cells to the public

METHODOLOGY

The study explores of the concept of creating new organs in Islam and the application of it in transplantation. For that purpose, the researcher have used the Qur'ān, Hadith, the works of Muslim scholars, particularly the works of theologians, scholars of Islamic law (fuqaha), and jurists (usul al-fuqaha) to describe and analyze the Islamic moral teaching and judgment on medical care, where textual analysis method was used.

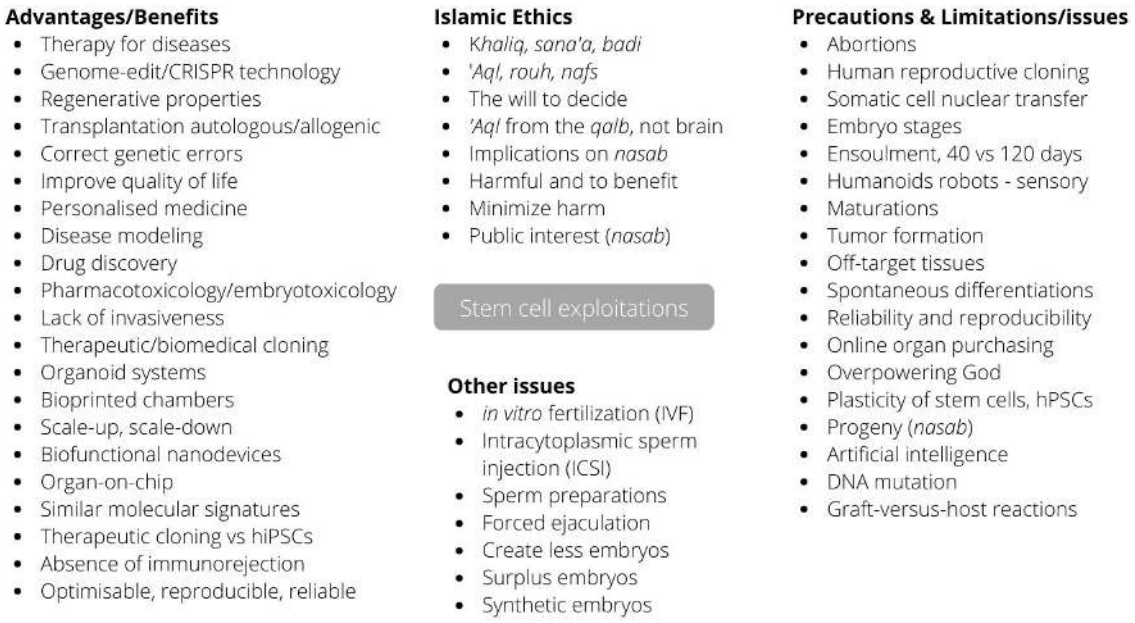

Figure 1 showing possible exploitations of stem cell technologies based on investigator's approach.

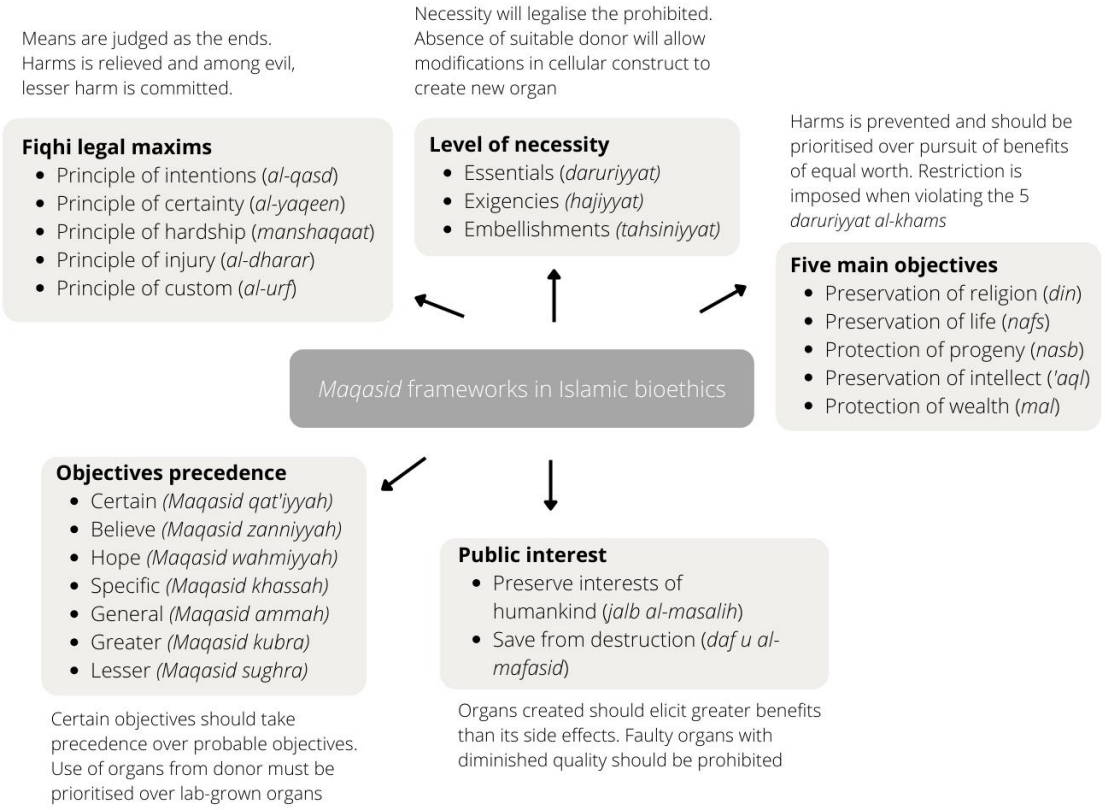

Figure 2 Integration of *Maqasid Al-Shariah* frameworks in stem cell-based organ synthesis

FINDINGS

1.Potential issues with new human-made organs

Since new organs are synthesised from human cell origin, a robust strategies should be implemented to ensure starting cells are in the best quality and suitable to be inserted into human body. Several considerations should be highlighted; 1) cells should be free from contaminating agents (i.e bacterial infections, mycoplasma), 2) absence of genome-integrating viruses that renders genetic stability, 3) ability to escape tumor events, 4) fully functional and mimic native organ phenotypes and 5) minimum adverse immunological responses.

For every cell division, it was reported that approximately one genetic modification or mutation occur. This will compromise the utilisation of stem cell-based therapy. It was also reported that stem cell are highly proliferative and easily sensitised to change in pH and extracellular environments. Thus, a single change in nucleotide base can alter normal transcription of DNA and eventually the epigenetic integrity. This is essential in maintaining survival and clinical benefit of stem cell therapy. Practically, these cells commonly been misused and pose significant risk in plethora of applications. This can be divided into short and long-term risk following therapy that include engraftment, survival, proliferation and regeneration of transplanted cells.

Another aspect worth to mention is that the manipulation of stem cells could change genomic stabilities, making cells to proliferate uncontrollably leading to tumorigenesis (Yoshihara et al., 2019). Also, this process may contribute to immunorejections and metabolic complications to neighbouring tissues. In another similar example, although it was reported that the use of mesenchymal stem cells (i.e umbilical cord) may create a reduced immunogenic graft-versus-host reactions, their applications should only be limited on paediatrics.

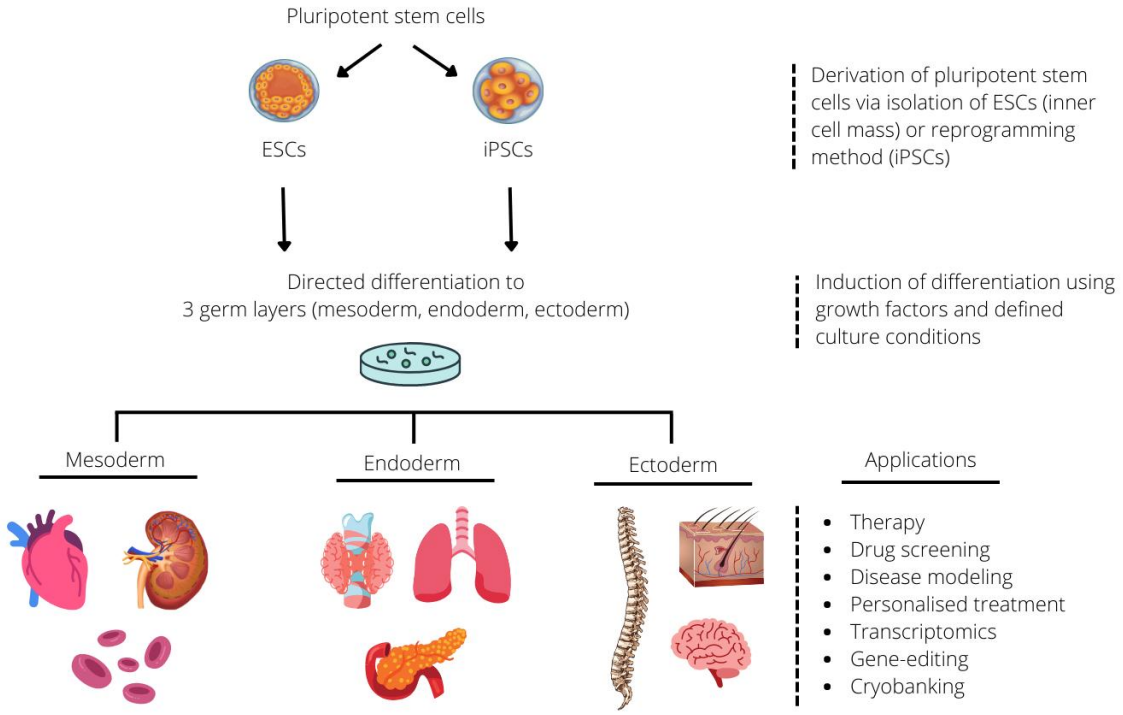

Figure 3 Directed differentiation of human pluripotent stem cells (PSCs) for organogenesis. Cells were endogenously stimulated with defined factors from multitude of protocols.

2.Fundamentals of Islamic ethics

Despite its enormous biomedical applications, research on stem cell-derived organoids should be carefully monitored and evaluated to avoid unwanted consequences. Possible alterations of genetic materials, tumor events and spontaneous differentiations should be scrutinised before allowing their clinical translations. Instabilities of genomic contents in organoids have been reported by several groups (Barkauskas et al., 2017; Kessler et al., 2015; Zachos et al., 2016). Therefore, safety profiles and quality control of PSC-derived organoids should be thoroughly examined. Maintaining highest quality of cells in culture will dictate its safe use in human.

From Islamic perspectives, ethics can be classified by four definitions. Firstly, *'amal salih* (good conduct) that are committed in accordance with *fitrah*, the human nature. It should create a distinction between righteousness (*al-birr*) and vice (*ithm*). Thus, the term *salihat* (proper) should not be used interchangeably with *sayyiat* (improper). In other words, *akhlaq* equated with human nature. Secondly, the ethics refers to religion, as seen in *Quran "So be steadfast in faith in all uprightness (O Prophet)- the natural Way of Allah which He has instilled in all people. Let there be no change in this creation of Allah. That is the Straight Way, but most people do not know" (Quran, 30:30).* Notably, Prophet Muhammad (*s.a.w*) said, *"the best among you are those who have best character and manners".* Thirdly, the *Quran* describes positive attributes of human persona as integral part of

human disposition, given by Allah. In contrast, negative attributes are the controlled by human desires. Finally, ethics covers both internal and external paradigm. Not only that, it encompasses intra- and interpersonal affairs of human. For instance, Islamic ethics encourage *tazkiyatun nafs* (self-purification). Simultaneously, men are obliged to socially respect other muslims and enjoin the spirit of brotherhood.

Ethics refers to set of standards that determines mans' action. This will include attitudes, virtues and duties of the individual to the society. Under certain circumstances, this can be associated with the customs, belief systems and traditions. Some may equate ethics to law and human feelings. However, being ethical does not necessarily abiding the conventional and accepting emotions. The definition of ethics should not be confined to any specific norms, behaviours or cultures where the whole society accepts. For instance in the cases of vandalism, homicide, dictatorship and corruptions. Regardless on the percentage of these immorality being practised in society, these habits remains wrongful in the eyes of communities and societies.

Current advances in science and technology may have indirect references in the *Quran* and *Sunnah*. The process of *ijtihad* (extracting and deriving sensible interpretations) were applied and on some circumstances, other sources of *fiqh* can be utilized such as *ijma'* (consensus), *qiyas* (analogical reasoning), *sadd az-zara'i* (blocking the means) and *istishab* (presumption of continuity). Similarly, *Maqasid* approach can be integrated to secure the benefits (*maslahah*) and preventing harms (*mafsadah*) (al-Qaradawi, 2013).

Good actions can be divided into three levels of importance; *daruriyat* (the essentials), *hajiyyat* (exigencies) and *tahsiniyyat* (embellishment). It was noted that the essentials are applied in order to preserve the five principles of *Shariah*; religion, life, lineage, intellect and property (al-Raysuni, 2006). In addition, *qawaid fiqhiyyah* (Islamic legal maxims) can be used to formulate ethical considerations. Most of contemporary research activities involve deliberation of harm and benefits that includes the five legal maxims of Islamic law; *al-'umur bi maqasidiha* (the acts are judged by their goals and purposes), *al-yaqin la yazulu bi al-shakk* (the certainty is not overruled by doubt), *al-darar yuzal* (harm must be eliminated), *al-mashaqqah tajlibu al-taysir* (hardship begets facility) and *al-'adah muhakkamah* (custom is authoritative) (Kamali, 2006).

3.Maqasid al-Shariah perspectives in organ synthesis

Synthesis of new organs should be evaluated in detail, considering whether or not it is classified under interfering or changing God's creation. It should be made clear that God is the absolute creator and humankind are the creation of God (*khalqillah*). Creating new organs are not considered as creating from nothing (God's attributes, *al-Khaliq*) but simply making new things from existed entities (*sana'a*). This illustrates the limited human intellects and capabilities. The making of new organs is not tampering with God's creation but rather providing alternative means

to protect human life. Importantly, there should be a clear distinction around issues relating to God's creation. This can be classified based on the level of importance; *taghyir daruri* (essential change), *taghyir haji* (exigent) or *taghyir tahsini* (embellishing change) (Hamdan & Ramli, 2018).

Maqasid al-Shariah has been coined by Imam Shatibi (d. 790 AH) to highlight preservation of the *din* (religion), *nafs* (life), *nasl* (progeny), *aql* (intellect) and *mal* (wealth). The first aim was to protect the religion via act of *ibadah* (worship) as essential component in preventing sins. *Hifz nafs* refers to preservation of life that govern security of individuals, mutual respect and improving quality of life. Protecting the progeny, *hifz nasl*, can be achieved by providing necessary health care for patients, newborn and infertiles. *Hifz aql* (preserving intellect) maintains intellectual growth and functions whereas *hifz mal* ensures a systematic wealth management and financial resources in a way that it can be fairly distributed (Kasule, 2004). Therefore, any actions violating these five purposes of *shariah* may be considered as unethical.

In this case, it is permissible to restore the normal function of organ by making a replacement organ to reduce physiological harm. In fact, making new organs can be a mandatory to restore human functions as *khalifah* and God servant. Transplantation of new organ to patients may extend the life of individuals and eventually a healthy offspring that can contribute to preserve the *din*. However, genetic enhancement (i.e implanting new skin cells for beauty gain) is not permissible as this fall under embellishing change categories (IIFA, 2007).

In the context of organogenesis, comprehensive approaches allow scientists to manipulate signaling cues and small molecule concentrations that can change stem cell morphology into a well-formed minute organs. However, the downstream signaling trajectories can deviate from the desired outcomes, leading to malformations in resulting organs. Different protocols for developing organs between laboratories across the globe have compromised the quality of organs. Therefore, despite the powerful properties of stem cells, standardised initiative should be initiated to ensure its applicability before translating into clinics. A sound evaluations to prevent misuse of unapproved clinical trials and therapy ensures its safety and reproducibility.

From *Maqasid* viewpoint, it can be critically implied that making new organ for medical means can be performed as this effort does not challenge God's creation, and in fact, are encouraged to lessen the burden of patients and preserve community interest at large. *In vitro* organogenesis should ideally be monitored, not only to protect the human live, but also offsprings. Genetic manipulation using CRISPR/Cas9 gene editing can alter DNA region and ultimately exacerbate social integrity by modification of heredity information. This however should be limited to model human diseases, not in therapeutics. Although this editing has not been approved in human embryos (except in Jiankui's unproven case), abrogating gene function should be confined to research-grade stem

cells, solely for education and research purpose.

Futuristically, if this treatment is approved for humanely use, considerations should be taken to protect the wealth, by granting ease of access to the public and free from financial constraint. It was reported that the stem cell treatments are dominated by private health-care providers which side effects of treatment highly likely to be under-reported. The cost of each treatments would be extremely overpriced that the public can even bear. The financial constrains may increase options of debt financing, mortgaging and bankruptcy. The psychosocial consequences are another possible outcome.

Therefore, the search for new organs must highlight the constant intellectual quest for a sound knowledge. Misuse of technological advances may incriminate human understanding and reasonings. Collectively, the *Maqasid* should be seen as the overarching principle that guide researchers to consider its benefits at larger scale, and when possible, generate less harm. Allah mentions, *"Do not cast yourselves into destruction"* (*Quran,* 2:195).

CONCLUSION AND RECOMMENDATION

It was essential to monitor the unforeseen risk that stem cells carry, the misconceptions on its use in medical settings and unproven mode of application. The existence of the 'grey-zones' between clinical settings and research innovations should not be misunderstood and overclaimed in order to approve implementations so that it would not be masked by the shadow of standard practice of medicine.

Islam does not oppose the *wasilah* (right means) and *ghayah* (motives) to create the real organs providing that the accomplishment may bring goods (*jalb al- maslahah*) and prevents evil (*dar al-mafsadah*). Generation of human-derived organs should be in accordance with *maslahah* (public interest). If these activities are not ethically managed, many patients are exposed to overstated promises making them vulnerable to unproven stem cell therapies. The treatment, however, should pass its clinical testing and proven to be safe and effective on human. Critically, insufficient transparency and accountability exposing the patients to public scrutiny. Production of 'off-the-shelf' organs in the future should predict impact on socioeconomic, health, laws and policies thus providing essential information for worldwide users.

RECOMMENDATIONS

The establishment of non-profit organisation, the International Society of Stem Cell Research (ISSCR), had issued 'Guidelines for stem cell research and clinical translation' which can be an acceptable common ground discussing the advantages and possible risks. However, lack of legislative approaches, politics and moral authority in this guideline require refinements of the contents. As an international consensus, the World Health Organisation (WHO) has outlined regulatory considerations in adopting stem cells under Article 21 of their constitutions that demand legal strategies in respective activities. This has further forced the United Nations Education, Scientific and Cultural Organization (UNESCO) to declare the Universal Declaration on Bioethics and Human Rights, a declarations to protect human integrity. It stated in Article 4 that 'In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected, and the personal integrity of such individuals respected' (Lenchuha et al., 2017). This declaration however does not monitor each exploitations as it does not

impose any duty on the government to protect human. It is solely depend on the government to execute their regulatory enforcements and preventing fraud.

Involvements of various policy-making institutions are detrimental to decide code of practice that are acceptable, safe and effective before issues relating to clinical practices and national laws can be implemented. Establishing a worldwide network under 'umbrella' of stem cell industry can facilitate cross-jurisdiction information sharing, identifying best practices and protect public safety as well as promoting evident-based discoveries. Consequently, Muslim countries can benefit from these unified guidelines before conducting stem cell research. However, the Islamic frameworks (Maqasid Al-Shari'ah) should be examined in order to categorise this action as a moral value and satisfy human function as Khalifah.

OUTPUT OF RESEARCH

1.Paper on 'Deconstructing Maqasid al-Shariah Frameworks in Stem cell-based Organogenesis' (Paper is under review of International Journal of Thought and Civilisation) 2022

2.Awareness Talk 1: Using stem cells to understand human organogenesis

3.Awareness Talk 2: Making new organs from human stem cells


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FUTURE PLAN OF THE RESEARCH

The study can be further simplified and summarised for general public use and will serve as supportive religious arguments by academic institutions, mosque authorities, public societies as an advocacy material. This research will potentially revisit current social and health policies to update the present established policy. Technically, this finding will be translated and developed into a concise and easy-to-understand messages. This work will pioneer, connect and bridge the collaborations between scientific communities and religious academics to delineate the ethics, advantages for medical sectors as well as potential exploitation on the use of stem cell technologies.

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