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Exploring the Islamic Perspective on Tissue Engineering Principles and Practice

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Abstract

Tissue engineering is related to the replacement, restoration, repair and/or regeneration of tissues/organs that are tailored to the needs of the individual patient. The potential applications of tissue engineering are being unveiled with much hype and expectations among the scientists and the public at large. The demand for engineered tissues may increase considerably, but the progress has been slow due to scientific and technical challenges that linked to moral, religious, philosophical, political and economic aspects. There are on-going debates on certain aspects that seem to indicate that scientists maybe "playing God". This article briefly analyses tissue engineering principles and the discourse surrounding it. Subsequently, the author briefly reflects on the Islamic perspectives, both for and against the technology. The discussions serve to provide a platform on how best to achieve a consensus that adequately deals with the scientific reality and the Islamic moral and legal jurisprudence that surrounds the technology.

Keywords: Tissue engineering, regenerative medicine, biomedical technology, personalized medicine, Islamic perspective

Introduction

Tissue engineering and regenerative medicine is a broad field encompassing principles from various disciplines that no single subject may deal with all of its aspects in meaningful depth. Regarded as a revolution in biomedical technology, tissue engineering was initially defined as an interdisciplinary field of research that applies engineering, health and life sciences principles. Together, they are used to develop biological living substitutes that restore, maintain, or even improve tissue or organ function (Langer & Vacanti, 1993). The terms "tissue engineering" and "regenerative medicine" may be used interchangeably, but they are more commonly being referred to as "tissue engineering and regenerative medicine" or "TERM" (Badylak & Nerem, 2010). Tissue engineering pathway for regenerative medicine (clinical application) hypothetically involves at least four distinct phases from bench to bedside i.e.

Phase I: Non-clinical experiment in the laboratory

Phase II: Pre-clinical / animal study for proof of concept

Phase III: Clinical trial involving human subjects

Phase IV: Regenerative medicine; clinical application

The overall approaches or pathway can be visualized as in Figure 1.

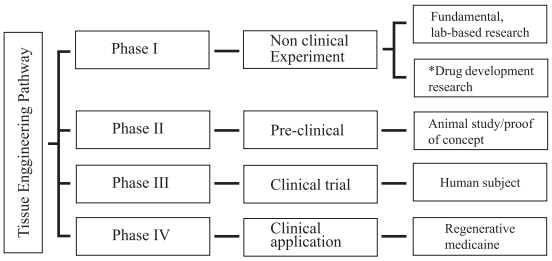

Figure 1: Shows a simplified tissue engineering pathway or approaches.

At the moment, TERM is in its infancy and plays a relatively small role in the actual healthcare settings. Various tissue-engineered medical products (TEMPs) such as tissue-engineered cartilage, bone, skin, bladders, small arteries and even a full trachea have been implanted in patients. However, those are still considered at experimental stages and not cost effective. Although more complex tissues or organs have been successfully reconstructed to certain extent by some researchers, they are still far from being fully reproducible and ready to be implanted into a patient. Despite all the uncertainties, the field continues to expand.

The production of TEMPs can be quite useful in other non-clinical research, especially in drug development. Investigations are being carried out to see the effects of medication

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candidates on functional TEMPs. The positive outcomes of these studies could expedite drug development and provide key tools for facilitating personalized medicine. If strategized accordingly, this approach can be more economic and lessen the use of animal models for drug research. Hence many benefits can be anticipated to be derived from TERM in terms of reducing harm and preventing disease. Muslims are encouraged to use their mental faculties to explore for ways to alleviate pain and suffering. However, those avenues are to be within the premise that any cure is from Allah (s.w.t)

"And when I am ill, it is He Who cures me" (Al-Quran 26:80).

Al-Madni (2013) opines that

"One of the blessings of Islam is that it never abstracts scientific programs or narrows the scope of the mind in the field of science and technology. Unlike other religions, there is no conflict between science and religion in Islam. Christian clergy opposed scientists, thinkers and pioneers of technology that we take for granted today. Many were punished, tortured and sentenced to death."

Indeed, there are other hadiths that indicate *Islam* encourages advancements in technologies to benefit Mankind. For example, the one narrated by Abu Huraira:

"The Prophet (pbuh) said, "There is no disease that Allah (s.w.t) has created, except that He also has created its treatment." (Sahih Bukhari Book: 76, Hadith: 5740)

The other hadith narrated by Usamah ibn Sharik:

"I came to the Prophet (pbuh) and his Companions were sitting as if they had birds on their heads. I saluted and sat down. The desert Arabs then came from here and there. They asked: Messenger of Allah, should we make use of medical treatment? He replied: Make use of medical treatment, for Allah has not made a disease without appointing a remedy for it, with the exception of one disease, namely old age." (Sunan Abi Da'ud Book: 29, Hadith: 3855)

Both hadiths above aptly describe the position of *Islam* with respect to looking for the remedy of diseases. One needs to understand that the obligation to seek treatment is not only on the sufferer (patient) but also on those who provides the treatment and those who have the means to study, innovate and formulate the remedy. In this way, the sanctity of life or at least the quality of life, is preserved as championed by the Islamic way of life (*Shari'ah*).

The potential applications of TERM, both for clinical and non-clinical purposes are being unveiled with much hype and expectations among the scientists and the public at large. Like any other technologies, the development of TERM is shrouded with opportunities and uncertainties. The demand for TEMPs may have increased considerably. However, the progress has been slow due to scientific and technical challenges that are closely linked to moral, religious, philosophical, political and economic aspects. Besides, there are on-going debates on certain aspects in TERM that seem to indicate that scientists maybe "playing God". Furthermore, the Islamic perspective on certain issues pertaining to research and application of modern biomedical technology is under-represented. There is a need to fill the gap.

Issues concerning organ transplantation, assisted reproductive technology, abortion, stem cell research and therapeutic cloning have been given much attention thus far. When compared to TERM, the deliberations involving those issues from the Islamic legal rulings are quite established. Thus, it is felt that the application of TERM should also be explored from the Islamic perspective.

This paper is not meant to be comprehensive but to give a brief analyses on TERM principles and the discourse surrounding it. The underlying strategies in employing selected

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cells, biomaterials and signalling factors for tissues or organs regeneration are discussed. The rationale for incorporating the genes into the cells or scaffolds and fabricating TEMPs for implantation is also covered. The authors intend to briefly reflect on the Islamic perspectives, both for and against TERM. This is done within the context of its principles and practices on whether or not the tissue should be produced *in vitro* or *in vivo* for implantation purpose and etc. The discussions are based on the concept of *ijtihad* that offers flexibility to examine and adopt new scientific developments and resolve issues in light of the *Qur'an* and *Sunnah*.

It is well-defined that the process of integrating Islamic perspectives into TERM requires deep awareness of both Islamic and modern philosophy of knowledge. Therefore, similarly to our previous work (Mohd Yusof et al., 2014), this paper distances itself from providing an ultimate Islamic decree in the application of TERM in healthcare. This effort, perhaps will provide a platform on how to achieve a consensus that adequately deals with the scientific reality and the Islamic moral and legal jurisprudence (*fiqh*) that surrounds the technology.

Principles of Tissue Engineering

The application of tissue engineering principles, by definition, considers the following three (3) main elements, (a) Cell sources, either differentiated or undifferentiated cells (adult versus embryonic stem cells); (b) Biomaterial scaffolds, either naturally-derived or synthetically-derived three-dimensional porous matrix; (c) Signalling factors or 'regulators' or 'bioactive agents', either physical stimulus such as mechanical loading, culture conditions and flow condition in vitro (bioreactors), and/or chemical such as cytokines or growth factors.

These elements, commonly known as 'tissue engineering triad' (Figure 2) may be used individually or in combination to engineer TEMPs for implantation purposes. The macro- and micro-architecture of a tissue is determined by adhesion mechanisms that involve "cell to cell" interactions as well as "cell to matrix" interactions.

In TERM, cells can be seeded and cultured onto a scaffold capable of supporting new tissue formation. The porous, three-dimensional absorbable biomaterial scaffolds and signalling factors serve to regulate cell growth and proliferation. Internal affairs simulation (biomimetic) will provide an optimum in vitro microenvironment for cells/tissues survival. Hence, the basic principle of TERM is to reconstruct biological spare-parts or living tissue graft (i.e. TEMPs) for the human body. Such new discoveries that help alleviate the suffering of humanity are welcomed in Islam.

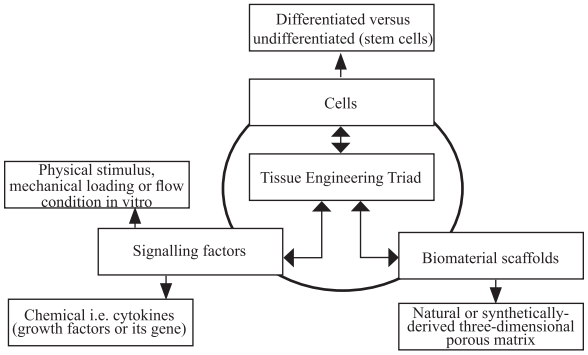

Figure 2 shows the 'tissue engineering triad', which represent the principles of tissue engineering.

However, with the advancement of biomedical technology and rapid scientific development, allowing the tissue graft to be developed *in vitro* may have an undesirable effect of devaluing biologically living tissues. This may lead to TEMPs being commercialized and produced as therapeutic products on purpose. In order to address the issues pertaining to in-vitro development of living tissues and commercialisation a decree issued in 1995 should be considered. At the 38th *Muzakarah* (Conference) of the *Fatwa* Committee of the National Council for Islamic Religious Affairs Malaysia, the council discussed on the use of tissue graft in medical practice and decided that: "(1). Tissue graft in medical practice is permissible; (2). Tissue graft usage is only for

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medical purpose; (3). Tissue graft cannot be misused for trading purpose or other purpose"

With those decisions in place, an examination involving the "tissue engineering triads" that make up TEMPs will now be presented.

Cell Sources

What types of cells are to be used as source of cells? Under what conditions cells should be expanded while retaining their specific phenotype in vitro?

Cells sourcing for TERM can be taken from autologous cells (harvested from the same person), allogeneic cells (harvested from a different person) and xenogeneic cells (harvested from a different species). The types of cell can be divided into differentiated cells (adult progenitor cells) and undifferentiated cells (stem cells). The difference between these two cells types is that, differentiated cells are specialized or committed cells that perform specific function such as chondrocytes in articular cartilage. While undifferentiated cells are uncommitted cells and will remain uncommitted until appropriate signals stimulate them to differentiate into committed cells. The needs for stem cells in TERM are due to inadequate supply of committed cells, morbidity at the donor site, and lack proliferative and biosynthetic activity of committed cells. Stem cells have the capacity to self-renew and to divide actively in *in vitro* culture. Stem cells can differentiate into multiple specialized cells types in the body and thus making them as suitable candidate for tissue regeneration and/or repair especially those unable to regenerate spontaneously after injuries (Stem Cell Basics, 2009).

Stem cells can be isolated from human embryo, foetal or adult tissues. Other than the isolation from inner cell mass of the blastocyst, pluripotent embryonic stem cells (ESCs) can also be derived from foetal tissue due to terminated pregnancies. To date, scientists and tissue engineers are still investigating whether differentiated cells and undifferentiated stem cells from adult tissues have the potential comparable to that of ESCs. In terms of development potential, ESCs are being reported to have greater differentiation potential than differentiated cells and adult stem cells (ASCs) (Murnaghan, 2014). While ESCs can differentiate into almost every cells lineage, ASCs may only develop into a limited cell types. However, recently ASCs were shown to have greater plasticity than they were initially thought (Chang et al., 2013). However, the remaining challenge, perhaps, is which cell source holds the advantage and the key for tissue regeneration?

At a glance, differentiated cells and ASCs hold a distinctive advantage. In a fully autologous system, a patient's own cells will be harvested, culture-expanded and re-implanted into the patient. There will be no issues on immune rejection since the cells are compatible with patient's own body. However, for ESCs, the recipient may require lifelong immune suppressive drugs to overcome rejection of the new transplanted cells. Both the differentiated cells and ASCs are adult tissues and obtained with consent from the patient. There may be little, if any, ethical issue on ASCs therapies compared to that of ESCs.

Controversies and endless debates involving the use of ESCs are due to the destruction of an embryo following cell isolation. The continuing deliberations have essentially become overwhelming and creating a contentious argument on abortion between religious leaders, scholars, politicians and the public (Fadel, 2012). Previously, Sachedina (2000) stated that "research on stem cells made possible by biotechnical intervention is regarded as an act of faith in the ultimate will of God as the Giver of all life as long as such an intervention is undertaken with purpose of improving human health". An Islamic decree that could have some light pertaining to the element of faith addressed by Sachedina (2000) can be appreciated from the Islamic *Fiqh* Council of the Muslim World

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League, during its 17th session held in Makkah (2003). The Council examined the stem cells issues and adopted the following resolutions,

"First: It is permissible to obtain, develop and utilize the stem cells for medical treatment or lawful scientific research, if the source is also lawful, such as the following: (1). Adults, if they have given permission and they are not exposed to any harm. (2). Children, if their guardians have given permission for some legitimate reason, and at the same time, these children are not exposed to any harm. (3). Placenta and umbilical cord, if the parents have given permission for that. (4). Miscarried foetus, for some lawful treatment purposes, and with the parents' permission. (It may be recalled that the Islamic Fiqh Council of the Muslim World League, during its 12th session adopted the seventh resolution on the cases in which abortion is permissible). (5). Surplus inoculums from the test-tube babies if available and donated by the parents on condition it would not be used for illegal pregnancy.

Second: It is not permissible to obtain and utilize the stem cells if the source is unlawful, such as the following: (1). A foetus that was deliberately aborted without any lawful medical reason. (2). Deliberate inoculation of an ovum and spermatozoa of the female and male donors. (3). Therapeutic cloning."

Further deliberations in the 67th *Muzakarah* (Conference) of *Fatwa* Committee of the National Council for Islamic Religious Affairs Malaysia discussed the ruling on therapeutic cloning and stem cell research. The decision adopted by the conference held in 2005 among others, "(1). Therapeutic cloning for medical treatment, for instance to create certain cells or to replace damaged organ is permissible. The act is permitted provided that the *Syar'ie* precautions are considered. (2). Using frozen embryo or extra embryo *in vitro* fertilization process is permissible for research purpose. However, permission must be granted from the married couple who are under treatment. The research on the embryo must be done before the embryo reach the '*alaqa* stage (blastocyst)."

However, it is important to note that, "Human cloning for whatever reasons is prohibited because it is against the nature of human creation that is decided by God."

This decision was adopted following the discussion on human reproduction and cloning from the *Shari'ah* point of view during the 51st *Muzakarah* (Conference) of the *Fatwa* Committee of the National Council for Islamic Religious Affairs Malaysia in 2002.

ESCs issues were also deliberated by medical practitioners and physicians during the Islamic Organization of Medical Science (IOMS) meeting and most of them concluded that ESCs research for therapeutic purposes including non-reproductive cloning is permitted and encouraged in *Islam* (Musa, 2006). Publications by the Islamic Medical Association of North America (IMANA) Ethics Committee (2007) and several other Islamic organizations added their approval for ESCs research (Fadel, 2012).

Hence, from the authorities presented above it can be concluded that both ASCs and ESCs are permissible within the Islamic framework as outlined. It is anticipated that scientists will be able to discover the full potential of differentiated cells and ASCs over ESCs for future therapeutic applications given the permissibility issues from Islamic perspectives are safely addressed.

Biomaterial Scaffolds

What types of biomaterial scaffolds should be used? What types of material of fabrication, appropriate mechanical properties, pore size, absorbability and etc.? How to manufacture the scaffolds? Or, what is the best method for scaffolds fabrication?

In TERM, cells and growth factors are certain, but biomaterial scaffolds may vary depending

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on the needs or design. It is believed that "nature" is the best designer for tissue or organ development. It has never been easy to manufacture scaffolds since good design for biomaterial scaffolds should bear a resemblance to the actual extracellular matrix of the tissue (Willerth & Sakiyama, 2008). Scaffolds are either natural or synthetics. They may be used individually or in combination to produce good scaffolds. Good scaffolds will direct cells growth and regenerate three-dimensional tissue. The naturally-derived biomaterials include protein-based and polysaccharide-based biomaterials. Due to their multitude functions in the human body, these proteins and polysaccharides hold great advantages that meet the requirements for TERM applications. Other than having suitable sites for cellular adhesion, natural biomaterials are usually biocompatible to the human body. However, the composition of natural biomaterials can be varied and uncertain. The purity of the protein-based biomaterials (e.g. collagen, silk and fibrin) or polysaccharide-based biomaterials (e.g. agarose, alginate, hyaluronan and chitosan-based scaffolds) must be carefully identified to avoid any post-implantation activation of immune response.

In terms of mechanical properties, the naturally-derived scaffolds usually lack mechanical strength (Munirah et al. 2007) and need to be optimized accordingly. Polymer-, peptide- and ceramic-based biomaterials are the most common synthetic biomaterials used in TERM. As an alternative to the natural biomaterials, these synthetically-derived biomaterials have defined chemical composition. This property facilitates reproducibility of the scaffolds in that, their mechanical properties, shape and degradation rate can be controlled according to the intended requirement. The synthetic biomaterial scaffolds can be tailor-made to meet specifications at the injury or implantation site. In TERM, mechanical properties are important to determine cell differentiation. However in drug developments, specific degradation rate is more important as it control the release (rate) of drugs incorporated into scaffolds. Unlike natural biomaterials, the synthetic biomaterials lack sites for cell adhesion. The sites have to be altered chemically to allow appropriate signals for cell adhesion and proliferation.

The suitability for *in vivo* implantation is subjected to the biocompatibility of the materials. Therefore, biocompatibility assessment of the materials and its by-product is essential to avoid any harms or complications such as unwanted immune responses that may be triggered in the host-recipient after implantation. At the moment, to ensure thorough safety assessment, biocompatibility testing can be done in accordance with the FDA (U.S. Food and Drug Administration) guideline. Other than safety issues, the origin of the materials should be observed and must not contain forbidden materials.

Abdul Rahman (n.d) highlighted that based on "sound logic" and Islamic teachings, the medical practitioner has no right to recommend or administer any harmful material or substance to the patients. It was also related on the authority of Abu Sa'id Sa'd bin Malik bin Sinan al-Khudri (RadhiyAllahu 'anhu) that the Messenger of Allah (s.w.t) said:

"There should be neither harming nor reciprocating harm" (Forty Nawawi, Hadith 32)

This hadith is a prime guideline for practitioners to ensure that no harm is meant to be introduced in the interventions. The use of permissible materials should be along the lines as evident in the Holy Quran (7:157),

"... and He makes for them good things lawful, and bad things forbidden ..."

There is a straight forward submission to *Allah* for He indicates in His Book that Man should abstain from those things that are bad. Failure to observe what He forbids will place man into His displeasure and the imminent penalties that awaits him in the hereafter. A good example of toeing the fine line between what

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is permissible and what is not in relation to the use of materials relates to one hadith narrated by Wa'il al-Hadrami, who reported that Tariq b. Suwaid a-Ju'fi asked the Prophet about liquor.

"He forbade (its use) and he expressed hatred that it should be prepared. He (Tariq) said: I prepare it as a medicine, whereupon he (the Holy Prophet) said: It is no medicine, but an ailment." (Sahih Muslim Book: 37, Hadith: 5256)

While the above hadith highlights the concern by Prophet Muhammad (pbuh) concerning liquor, practitioner involved in TERM should take heed and take the necessary steps to ensure that the materials used are within the limits of permissibility as espoused by the religion. This is due to the fact that some amount of leverage can be found when a situation calls for considerations based on "out of necessity". A Qur'aanic verse that attests this can be found in the Holy Qur'aan where Allah says,

"He hath only forbidden you dead meat, and blood, and the flesh of swine, and that on which any other name hath been invoked besides that of Allah. But if one is forced by necessity, without wilful disobedience, nor transgressing due limits - then is he guiltless. For Allah is Oft-forgiving Most Merciful." (Al-Quran 2:173)

The amount of leverage based on the word "necessity" could lure practitioners to take swift decisions to allow permissibility, while avenues to render the "necessity" permissible have yet to be exhausted. The practitioner is cautiously reminded of this possibility.

Signalling Factors

What are signalling factors required to stimulate cell proliferation and matrix synthesis or even to facilitate differentiation of stem cells?

The governing principle of this part is that, cell fate is influenced by cells' interactions with components of their microenvironment. Cell fate is believed to have strong association with culture conditions. Cell differentiation requires optimum physiological conditions such as temperature, pH, oxygen, three-dimensional environment, and adequate cell-to-cell contact. Biochemical factors (e.g. nutrients and growth factors) and physical stimulation (e.g. compression and tension) are important to direct proper cell growth and differentiation. Inadequate signalling factors will lead to loss of specialized function, cells senescence or aging and, eventually cell death. The signalling factors may include soluble and immobilized factors, the extracellular matrix (*see* biomaterial scaffolds), and signals presented by adjacent cells. In cell culture basis, defined culture media induce cell differentiation by providing key regulatory factors.

Dynamic culture system such as bioreactors improve cell seeding and functional tissue development by providing mixing, mass transport, and biophysical stimulation. This microenvironment simulation is critical for proper expansion of cells *in vitro*. This is particularly important for both basic and translational research in TERM.

Gene transfer approaches have been introduced for TERM applications due to inefficiencies of protein delivery *in vitro*. The difficulties of protein delivery include short biological half-life, ineffective localisation, rapid withdrawal from application site, higher dosage required, unwanted side effects and very costly. To overcome these issues, gene transfer offers a more efficient management of protein delivery by means of independent protein regulation. The advantages of gene transfer include the ability to sustain and regulate the endogenous synthesis of gene product, efficient localization, and greater biological potency with multiple genes transfer. In practical, gene transfer can be done in situ with minimal scaffolds required.

Genetic engineering is one of the greatest discoveries in modern science nowadays. Its applications (e.g. cloning and recombinant

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technology) enable us to synthesize growth factors or its gene and hormones (e.g. insulin that was previously taken from pig) for both research and clinical treatments. Gene transfer involves cloning and thus part of genetic engineering. If the combination of gene transfer and tissue engineering approaches is successful, a simple, cost effective, expedited tissue restoration may be achieved using a single intraoperative procedure as indicated in Figure 3. The illustration is for osteochondral treatment that intend to use gene transfection procedure using identified vector into the harvested mesenchymal stem cells. The transfecting cells will be then incorporated with a suitable biomaterial scaffold and transplanted into the defect. It is anticipated that the resulting cells-scaffold complex will be able to regenerate and achieve complete tissue reparation. It is also believed that this single intraoperative procedure will reduce harm to the patient.

As indicated in the previous sections, therapeutic cloning for medical treatment, for instance to produce certain cells or to replace damaged organ is permissible. Such developments are commendable in Islam. However, more research has to be done before it can be applied into humans. This is to highlight that through research the intensity of certainty can be improved.

Based on the concept of Evidence Based Practice, no intervention can be applied unless proven that the benefits outweigh the risks. The knowledge base grown from research should be ample enough to provide an element of certainty that the intervention is carried out by an authority; one who has the necessary knowledge and competencies to undertake the procedure. It was narrated from 'Amr bin Shu'aib, from his father that his grandfather said:

"The Messenger of Allah (s.w.t) said: 'Whoever gives medical treatment, with no prior knowledge of medicine, is responsible (for any harm done)." (Sunan Ibn Majah Book: 31, Hadith: 3595)

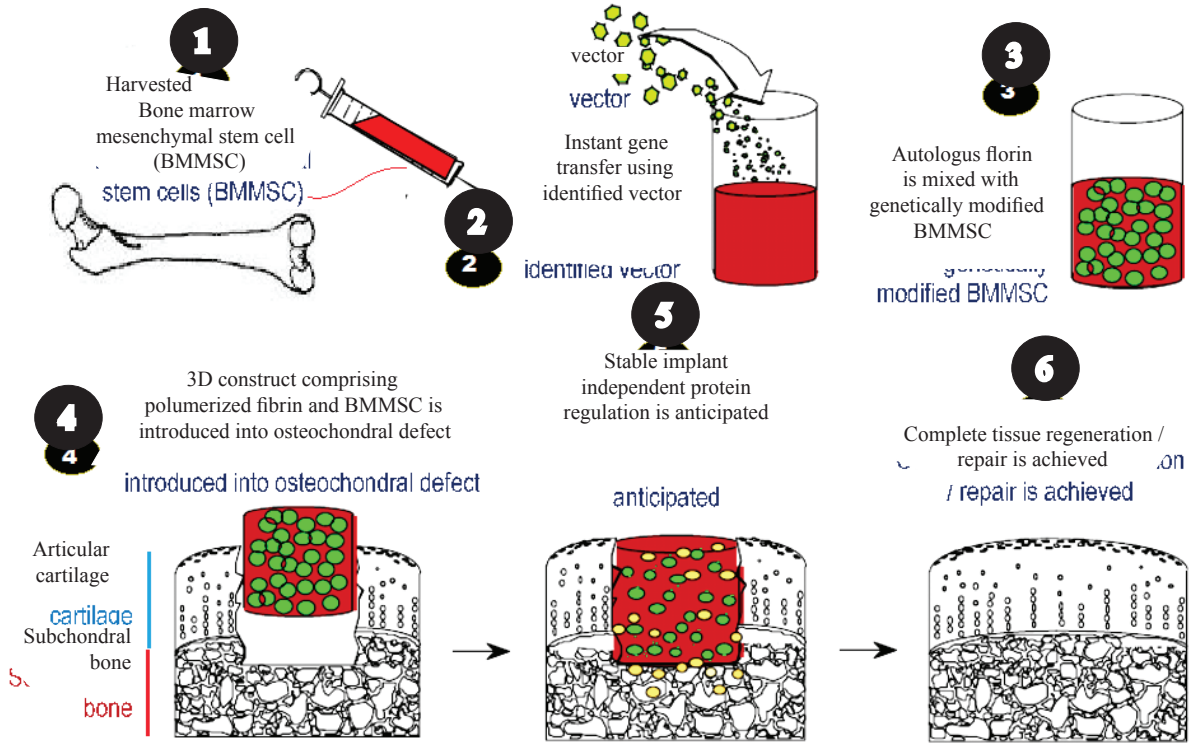

Figure 3: Represents a simple gene transfer steps for (osteochondral) tissue engineering.

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Conclusion

Fundamental research and scientific development reveal the potential of TERM applications. However, a significant number of unanswered questions about the actual requirements for tissue regeneration, the mechanisms associated with its pathophysiology and the unresolved ethical issues remain as challenges to the field. The development of modern biomedical technology poses complex questions for Muslims; the answers to which we are still seeking. Dr. Shahid Athar (n.d) in his book stated that,

"The Muslim masses are ignorant and naive, behaving like the bird which, fearful of its enemies, buries its head under the sand, thinking that it is safe. Muslims are split in two groups. One group is educated and modernized and accepts anything that serves science and humanity, irrespective of religious or moral laws that might be broken. The other group of so-called Islamic scholars have knowledge of Islam, but not of medical sciences. They are quick to give their opinion on everything. However, both groups should be reminded that Islam is not a religion of personal opinions."
From the discussions presented in this paper, the authors felt that all aspects of TERM have yet to be considered in details. *Islam* demands from us a sincere and continuous effort to achieve growth and development in research and knowledge pursuit. These are done, first and foremost, to please *Allah*, and secondly to realize our own welfare in both our worldly and religious lives. Muslims must be ready with the necessary knowledge to engage the challenges that confront them. The fast pace of technology requires the Muslim practitioners to be not only well versed in his field but also in the field of theology and Islamic Jurisprudence. This is to enable the Muslim practitioner in his quest, for the betterment of Mankind, is indeed conducted within the framework of the religion. No matter how great the achievement one could have, one should remember that everything in this world are at the decree of *Allah*. Abu Khizamah said: "The Messenger of Allah (s.w.t) was asked: 'Do you think that the medicines with which we treat ourselves, the Ruqyah by which we seek healing, and the means of protection that we seek, change the decree of Allah at all?' He said: 'They are part of the decree of Allah.'" (Sunan Ibn Majah Book: 31, Hadith: 3563)

Finally, amidst all the technological wonders that Man can deliver, the guidance that he should seek is based on the two revealed sources, the Holy *Qur'aan* and the Hadith. The authors wish to caution their fellow brethren that sincerity in addressing Islamic perspectives in their professional environments always be preceded by what *Allah* says in the *Qur'aan*,

"It is not fitting for a Believer, man or woman, when a matter has been decided by Allah and His Messenger to have any option about their decision: if any one disobeys Allah and His Messenger, he is indeed on a clearly wrong Path." (Al-Quran 33:36).

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