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Genetically Manipulated Pigs in Xenotransplantation: *ḥaram* or *halāl*

Dr. Kee Lam Wong [1], Prof, Waleed Fekry Faris [2]

1- *MBBS (HK) MTH (Queensland) MD (HK) FRCP (Edin) FRACP FHKCP FHKAM (Medicine) - Rheumatologist in Private Practice (Hong Kong) andInternational Institute of Islamic Thoughts and Civilization, International Islamic University Malaysia, Kuala Lumpur, Malaysia.*

2- *PhD, Virginia Tech University, USA; MSc and BSc (Mechanical Engineering), Zigzag University, Egypt. - Professor Dr, International Institute of Islamic Thoughts and Civilization and Department of Mechanical Engineering, International Islamic University Malaysia, Kuala Lumpur, Malaysia.*

Correspondence: Dr Kee Lam Wong wongkl7352507@gmail.com

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Abstract

Allotransplantation (AT) is the accepted mode of treatment for patients with organ failures. Perpetual (human) Organ Shortages in developed and developing countries limit the number of patients that can benefit from this treatment. In addition, organ shortages create enormous ethical controversies, illegal activities and possibly injustices. Xenotransplantation (XT), especially porcine xenotransplantation (PXT), may provide the solution to Organ Shortages and solve their consequent ethical problems.

Recent advances in genetic manipulation (GM) of the porcine donor genome and blastocyst complementation (BC) have the potential to ameliorate or abrogate the obstacles to human PXT. Once PXT is successful in clinical transplantation, Organ Transplantation(OT) will enter a new era.

From the Islamic perspectives, opinions are divided on use of therapeutic products or organs derived from the pigs. *istihalah* (transformation), *ḍarūrah* (dire necessity) and *maṣlahāh* (public interests)have been applied in deliberations and decisions to permit such utilization. This paper reviews the prohibition and permissibility of GM in porcine biomedical products and organs with special emphasis on porcine knockout, porcine transgenesis, human-porcine chimera and animal welfare in PXT.

Introduction

Shari'ah governs the life of Muslims to ensure that the purposes of human creations are fulfilled in this world and hereafter. This entails the coverage of public interests and all humanities [1]. *Shari'ah* laws have entrenched flexibility to avoid hardships or injuries such that Muslims do not have to suffer physically or mentally to be compliant with these obligations, rules and regulations. [2].

halāl is what is/are permissible and lawful whereas *haram* is what is/are prohibited and punishable. The Qur'an prohibits the consumption of pork (Al-Baqarah 2:173; Al-Ma'idah 5:3; Al-An'am 6: 119; Al-An'am 6:145; An-Nahl 16:115) and arguably, all products related to pigs. Conditional permissibility is allowed when *is it halah* (transformation), *ḍarūrah* (dire necessity) or *maṣlahāh* (public interest) is accepted.

Human Organ Shortages in AT cause enormous medical and bioethical controversies and illegal activities. Pigs are the preferred donor animals in human-XT because of anatomical and physiological compatibility with potentially rapid and unlimited supply [3]. GMs provide the much-needed technology to overcome the obstacles to PXT [4]. Successful PXT will revolutionize the whole field of OT. What have been judged as *ḥaram* may become *halāl* if successful PXT is attained.

istihalah, *ḍarūrah*, *maṣlahāh* and permissibility of *ḥaram* treatment

The objectives of the *Shari'ah* are aiming for the welfare and benefits of the person, ummah and community at large. It is not penalizing and scaled. Derived from *Shari'ah* is *maqāṣid shari'ah* that was initially established for the purpose of protection of the five hierarchical necessity higher objectives: *al-dīn* (faith), *al-nafs* (life), *al-'ird* (dignity or progeny), *al-'aql* (intellect or mind) and *al-māl* (property or wealth).In addition to the necessity (*ḍarūrī*) *maqāṣid*, Padela introduced two complementary*maqāṣid*:needful (*ḥājī*) *maqāṣid*and the enhancing (*taḥsīnī*) *maqāṣid*[5].

Two common mechanisms are used in bioethical deliberations to reverse treatments from *ḥaram* (prohibitory) to *halāl* (permissible):

a) *istihalah*: the *ḥaram* products or ingredients have undergone a transformation process that changes their (phenotypic) appearances; physical, chemical, biochemical or genetic properties; identifiable characteristics or mode of applications [6] [7]. Sufficient dilution, minute quantities or unavoidable contamination may also make such products or treatment permissible [8] [9] [10].

b) *ḍarūrah*: the basis of *ḍarūrah* is the protection or preservation of the necessity *maqāṣid shari'ah*. If the pre-conditions for *ḍarūrah* are satisfied (Table 1), a prohibited treatment becomes permissible (*halāl*).

The often-under-emphasized issue in *ḍarūrah* is the effects of the medical condition(s) beyond the person. In Islam, *maṣlahāh* refers to something good that could bring benefit to the doer in this world and the hereafter [11].These include the interests (benefits and harms) of the person, the ummah and community at large. However, *maṣlahāh* does not give a blanket approval for permissibility. The application of *maṣlahāh* must be extremely careful, may be restricted and must not be used to create a separate unprincipled legal system on their own. Any deviation from or suspension of *Shari'ah* laws because of public interest (*maṣlahāh*) must not contradict the higher moral values of *Shari'ah*[12].

Organ shortages have resulted in numerous bioethical issues. Some of these can amount to injustice. These include:

a) Long waiting lists that prolong unnecessary sufferings, disease burdens on the person, caregivers, family, community and nation.

b) Patients dying while on the waiting list. About40% of patients on kidney transplant waiting lists may die in 5 years[3]and 43% of patients waiting for heart transplant died or become too sick for a heart transplant [13].

c) Strict inclusion criteria for AT that exclude patients with milder but medically significant organ failures.

d) Exclusions for AT that are based on age, co-morbidities, HLA sensitization etc.

e) Illegal activities e.g. organ trading, trafficking, duress, exploitation, transplantation commercialism, transplantation tourism, forced organ harvesting etc.[14] [15] [16] [17]. The sales of organs from Muslim and non-Muslim citizens of poor states, refugees and migrant workers etc. are well known with numerous anecdotes. These types of transplanted related crimes are often under-reported and are estimated to occur in 5 – 10% of global organ transplants [15].In 2018, about 40 million of people were victims of 'the trafficking of human beings for the purpose of organ removal' [16].

f) Controversies in definition and acceptance of brain death or donation after circulatory determination of death (DCDD) that facilitate human organ procurements [18].

If PXT is successful, porcine organs become tradable commodities and available to all the patients with organ failures. The potentially unlimited supply of organs could satisfy the demands for OT and solve these bioethical

issues. For Muslims, PXT can stop the procuring of human organs from living or deceased donors; eliminate the black markets for human organs and the exploitation of the under-privileged Muslims; avoid the controversies of brain death [19] or DCDD and provide much needed justice to all the patients.

Porcine derived treatment: overview and established permissibility

Pork is *ḥaram*. However, a wide range of porcine derived products and appliances are permitted to be used medically for a long time. In the contemporary period and during the life time of the Prophet, PBUH, pigs were grown and bred as source of food (pork) and hide. It is not envisaged that pigs can be used for other purposes, as known today. The often-quoted harmful effects from pork or pigs, including various porcine transmissible diseases [20] could be controllable or eliminated through meticulous porcine husbandry (*vide infra*) [21]. The metabolic effects from ingestion of pork or porcine organs, like hyperlipidaemia and gout, will not appear in recipients of Organ PXT. It is arguable whether these reasons could still be used to reject PXT.

The jurists' opinions are divided whether porcine derived biomedical products or treatments are *ḥaram* or *halāl* [20]:

a) *ḥaram*: pork and all porcine products are prohibited.
b) *halāl* after *istihalah* or *ḍarūrah* invoked [8].
c) *halāl* for *maṣlahāh* where benefits exceed the harms.

The extent of application of these general principles varies. A minority jurist school (Zhiri) opined that only pork is *ḥaram*. Other porcine products are permissible. *shāfi* and *ḥanbalī* schools limit the application of *istihalah* to a few circumstances only e.g. wine to vinegar and tanned animal skins [8]. However, most scholars permit the use of non-*halāl* ingredients in medications or treatments through *istihalah*. Where *istihalah* is disallowed, *ḍarūrah*or *maṣlahāh*is applied to permit*ḥaram* treatments in specific situations. In using *maṣlahāh*, the negative impacts of the harmful porcine xenozoonoses need to be excluded as well.

Porcine therapeutic products or appliances,that have been permitted,include porcine heart valves that are used for respective valvular replacements [20] [22], Clexane in post-partum women [23], gelatin in vaccines and capsules, and trypsin in vaccines [6] [7], porcine surgical products [24].

Cells and Organs PXT: Compatibility and Obstacles

As in all OTs, successful PXTs must overcome the various obstacles listed in Table 2.

From the Islamic Perspectives, PXTs also have to satisfy the requirements involving the recipients, donor pigs, the PXT process and the community at large (Table 3). In Islamic bioethics, avoidance of harm presides over benefits. Specifically, the first priority in PXT is the minimization or prevention of porcine xenozoonoses that may affect the recipients or spread to the community [5] [25] [26]. Researches will not be permissible if there were harms or violation to the rights of the patients, the community at large or the donor animals [11][27].

For both Cells and Organ PXT, GMs in pigs can enhance the survival and functioning of the Porcine Xenograft (PXG). More and more GMs have been investigated and are available for experimental and clinical studies [4] [28].

The often-neglected issue in PXT is the requirement of good animal husbandry [29]. The veterinary staff and facilities are responsible for taking care of the pigs from isolation and breeding to ova, zygote and blastocyst extractions, post-procedure care, operative delivery, early colostrum weaning etc. [21] Appropriate considerations to the welfare of animals must be given [30]. The animals after GM must be able to live well, have close to normal physiologies, survive and reproduce [31].

However, the more the GMs, the more the porcine genome will deviate from the wild type. This may affect the livelihood and welfare of the donor animals *per se*. Deleting some genes, e.g. SLA class I genes, may increase the risks of infection or cancer in the host animals [32]. Respective human genes are increasingly added to the pig genome to produce the more desirable human proteins. These pigs become more humanized and may have increased risks of trans-species microbe mutations and contracting human pathogens. Thus, over-zealous GMs may not be beneficial and should be avoided.

Genetic manipulations in Pigs: ḥaram or halāl

From the Islamic perspectives, all scientific researches, advances and developments must conform with Islamic ethics as prescribed in the Qur'an, hadiths and sunnah;

and be compliant with *Shari'ah* [27] [33]. Researchers should have bravery, honesty, consideration, experience, fairness and justice, and be knowledgeable. In simple terms, GMs in pigs have to follow 'the process of evidence, justification and truth' [30]. The process of deliberations for GMs will involve determination of permissibility from the source, the process and outcome of GMs to their clinical benefits and harms.

The techniques for GM have evolved rapidly over the last 30 years. Clustered regularly interspaced short palindromic repeats associated with protein 9 (CRISPR/Cas9) revolutionizes the whole field of GM and is the most promising and efficient technology that can be applied to PXT [28] [34]. Two predominant GM groups are available: knockout (KO)/deletion and transgenesis (TG)/addition [4] [28]. The success of PXT will be built upon these multiple and efficient genetic editing in the porcine genome in both the Conventional Approach and Human-Porcine Chimera (BC).

1. PXT: Conventional Approach

The Conventional Approach uses GMs to modify the porcine genome to improve PXG engraftment and survival [35] [36] [37], enhance physiological compatibility and ameliorate post-PXT syndromes [35] [38],eliminate or minimize risk of PERV infection [39] [40] [41].

However, GMs alone are not sufficient. Adjunctive immune-suppression or immune-modulation are required. The two thymo-kidneys, 'immunomodulated PXG', from Genetically Manipulated Pig (GMP) in a recent report were functional with no evidence of rejection 54 hours after PXT in the decedents (per protocol) [42]. KO will affect viability of the donor pig. TGs, that humanizes the donor's genome, may create ethical problems. Optimizing the GM combination, immunosuppression and/or immunomodulation protocols has to be determined in future clinical trials.

2. PXT: Human-Porcine Chimera (BC)

Post-PXT immunosuppression in PXG recipient is an important adjunct to successful PXT. Because of the Xenobarrier, the immunosuppression is expected to be very intensive even after GMs. The side effects of these immunosuppressive agents could be serious affecting the survival and quality of life of the recipients. Even in AT, 40% of death in kidney AT recipients died with a functional kidney allograft with most deaths attributed to immunosuppression [43]. Personalized or custom-made chimera that does not require such immunosuppression will be a better alternative especially for patients who cannot tolerate intensive immunosuppression.

The BCtechnology involves getting donor cells sourced from GMP with the critical gene for formation of the desired or target organ being knocked out (the agenesis phenotype). These are used to form the embryo. The host blastocyst is extracted and pluripotent stem cells (PSC) or induced PSC (iPSC) from the anticipated recipient is injected into the blastocyst. The PSC/iPSC will supply the missing (emptied developmental niche) organ genes in the host embryo and form the target organ. The resulting human-porcine chimeric organ is predominantly human with varying proportion of porcine cells. Being a chimeric organ, it is recognized as self by the recipient's immune system, is not rejected by the recipient andfunctions like an autograft. Post-PXT immunosuppression is not necessary. However, this method is still experimental and no human organs have been grown successfully yet [13] [44].

3 GMs in PXT: ḥaram or halāl

A simple statement to decide whether GMs in PXT is ḥaram or halālisprobably not desirable or possible. A careful dissection of the entire process of GMs and PXT would be needed to determine their permissibility. The foremost and critical issue is how successful is the Organ PXT. From the Islamic perspectives, PXT is permissible only after invoking istihalah, ḍarūrah or maṣlahāh. Benefits from PXT in recipients with the respective organ failure must be established to decide on the permissibility of GMs, i.e, the post-GM PXG needs to be successfully engrafted and functional, relieving the suffering of the recipient.

3.1 General Considerations

There are no published deliberations or decisions with regards to permissibility of GM in PXT. GMs are linked to experimental and clinical PXT for permissibility. Four linkedgroups need to be assessed: i) the pig (donor or source animal);ii) the GM process; iii) the post-GM PXG; iv) PXT recipients and the community at large.

To be permissible, animal welfare before and after GMs needs to be well taken care of in biosecured facilities. Rules, regulations and guidelines must be established and

complied with suchthat the rights of the donor pigs are protected [37] [42].

The GM process starts from the donor (porcine) cells to the mature GMP. The CRISPR/Cas9 system does not involve any (Islamic) unlawful materials. Even if unlawful materials or procedures are used, *ḍarūrah* can be invoked. This follows the general principles established in the use of unlawful or prohibited (porcine) ingredients for medical use e.g. alcohol in liquid medicine, gelatin in vaccines etc. [6] [8] The GM is needed for the PXG that is used either for research or clinical studies. If the unlawful material or procedure is absolutely necessary to complete the GM process and no lawful alternative is available, they will be permitted through *ḍarūrah* for 'future' public interest.

The third and fourth groups comprise the full process of PXT from PXG to the recipient and community at large. Similar to organ transplantation [45] and porcine products [8], three views are expected on permissibility of GMs in PXT:
a) Categorically impermissible (all *ḥaram*).
b) Impermissible in principle (*ḥaram*) but can be conditionally permissible (*halāl*).
c) Generally permissible (*halāl*) under certain conditions.

3.2 GMs: Impermissibility

The impermissibility view establishes its view on the general prohibition of pork and all porcine related products, including porcine organs, irrespective of how these are produced or used [8]. Similar to any other OTs, this harm would outweigh all benefits obtained in this life and hereafter [45].Thus, all porcine organs, wild type or after GMs, are impure and not transplantable into Muslim patients for whatever reason.

3.3 GMs: Conditional Permissibility

GMs is likely to be mandatory for PXT to succeed. Humanizing the porcine genome e.g. human insulin or erythropoietin, to produce humanized protein may infringe on human creation as well. The conditional permissibility view relies on the relieves given by the Qur'an and *ijtihād* that abrogates porcine prohibition and any contradiction to human dignity. These relieves may be *istihalah* or *ḍarūrah*. *istihalah* cannot be invoked since GMPs are still predominantly porcine. If *ḍarūrah* can be invoked for PXT in patients with organ failure, it can be similarly invoked in GMs and *vice versa*.

To invoke *ḍarūrah*in PXT, the preconditions for the medical condition (harm) and availability of the prohibited treatment are clearly satisfied (Tables 1 and 3). However, the benefits are not established. As of now, the most successful PXT is Islet PXT for type 1 Diabetes Mellitus (T1DM). Other organ PXTs are still experimental though they appear promising for kidney and heart PXT. Nevertheless, out of beneficence and altruism, the recipients may receive the GM-PXG in experimental PXT after knowing the harms, possible benefits to himself or future benefits of other patients with organ failure (*maṣlahāh*). Since GM plays the pivotal role in the current experimental and clinical PXT, it would be permissible accordingly through *maṣlahāh*.

3.4 GMs: General Permissibility

The general permissibility view uses*maṣlahāh* (human interests) to support that PXT is needed for Muslim patients with organ failure and the community at large. The enormous benefits of GM-PXT to the public for solving the injustices, unethical and illegal activities in Muslims and non-Muslims arising from Organ Shortages could over-ride any prohibitions. The minority opinion from Zahiri School that only pork is *ḥaram* and aall other parts of pigs are *halāl* would also support General Permissibility [8].

3.5 GMs: Special Considerations in BC

BC after GM is experimental and not ready for clinical application. Permissibility will need to be decided in the future. The first requirement for permissibility of BC is to create a totally human target organ. From Islamic perspectives, inserting any piece of human genetic information into the pig's genome contradicts the purpose and dignity of human creation. In addition, the personalized chimeric human organ will not be completely human. The purity status of the chimeric organ is debatable, especially on lawful procurement or slaughtering of 'a humanized' animal, and permissible extent of porcine component in the chimeric organ. Minute quantity of porcine cells or fluid can be considered as dilution within the meaning of *istihalah* [8] [9] [10]. *Ex vivo* perfusion of the target organ by 'preparatory' fluids can minimize the porcine elements further by removing the impermissible porcine blood and

fluid within the target organ. Nevertheless, these 'contaminated' or 'residual' porcine components may still be considered *ḥaram* and will require *ḍarūrah* to make the chimeric organ permissible [46].

Furthermore, all unwanted differentiations and migrations from PSC to the brain, gonads or elsewhere have to be eliminated by appropriate GM technology (suicide genes) [47]. To minimize the risk of harm of PERV to the recipient and the community at large, low PERVs and/or PERV-C free GMPs should still be chosen [48].

Conclusion

The public interests on Organ Shortages and associated ethical issues are immense especially in Muslims and non-Muslim countries. If PXT is successful and permitted, transplantable organs become easily available. Most bioethical controversies, including illegal and unethical organ procurements, can be eliminated.

The foundation of any successful PXT is GM. Post-GM Organ PXTs still require adjunctive immunosuppression, immunomodulation or tolerance induction (chimerism) [32].BC is a promising approach for PXT where GMs are also required. Besides its intrinsic advantages over the conventional approach, it could provide a potential alternative to liver PXT which medical problems are extremely difficult to overcome by conventional GMs.

As of now, *ḍarūrah* cannot be invoked to allow permissibility of GM because benefits from PXT have not been established. At this stage, GMs in pigs can be permitted on *maṣlahāh* for both experimental and clinical PXT until PXT benefits are certain or established. By then, *ḍarūrah* can also be invoked permitting GMs and PXT.

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Table 1 Preconditions for *ḍarūrah* [2]

1 The medical condition

a) affects his/her life at this moment (immediate) or near future with high certainty or probability.

b) causes his/her life in danger or shorten his life expectancy.

c) inflicts physical, social or psychological suffering, pain or agony.

d) has negative impact on his/her quality of life (well-being) if the harm is allowed to continue.

e) improves or will be benefited from a prohibited medical treatment.

2 The prohibited treatment

a) is effective or likely to be effective to preserve or save life; relieve suffering, pain or agony; improve his/her quality of life.

b) is the best option after a thorough harm-benefit, what-if and proportionality analysis.

c) is the only option with no other lawful treatment being available.

d) is accessible, affordable and executable.

e) is provided by a trusted experienced and Allah-fearing medical practitioner.

3 The execution of the prohibited treatment

a) will not inflict harm on other people or conflict with other hierarchical necessities in *maqāṣid shari'ah*.

b) must be target based with the minimal effective amount for the shortest possible period.

c) must minimize the cause of prohibition as much as possible.

d) will be stopped once the harm or the anticipated harm has resolved or a lawful treatment is available.

Table 2Obstacles following PXT

Survival Phases after PXT	Obstacles
Immediate	Structural and technical compatibility Complications from Transplant Operation Hyper-rejection
Short-term	Rejection Acute infection from immunosuppression Physiological incompatibility
Medium-term	Rejection Dysfunction PXG Post-PXT syndromes Opportunistic infection Cross-species infection
Long-term	Chronic rejection Dysfunction PXG Post-PXG syndromes Opportunistic infections Cross-species infections

Table 3 Anticipated Requirements for PXT: Islamic Perspectives

1 The Recipient:

a) he/she must have suffered significantly from one or more organ failures.

b) he/she has consented to PXT.

c) the acceptance or tolerance of risks is personal and subjective.

2 The Pig:

a) Respective organs are available.

b) Rights and welfare are safe-guarded.

c) The procurement process should only cause minimal suffering to the pig.

d) The aftercare following procurement should dignify the pig with strict infection control.

3 The GM and PXT process

a) PXT is the only method available to the recipient.

b) PXT has a reasonable chance of success and provides benefits to the recipient through a functional organ relieving his suffering and saving his life.

c) The harms and benefits of the PXT must be compared to the natural state and history of progression of the organ failure, supportive therapy and AT in the recipient.

4 The Public

a) The Public will not be harmed by porcine related xenozoonosis.

b) The Public can benefit from PXT with less disease burdens and less public health expenses used for treatment of patients with organ failures.

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