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Review Article

Gene Modification in Non-Human Animal for Developing Human Compatible Organs: Ethical, Legal, Clinical and Societal Issues

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Abstract: CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) as a gene editing tool is a precise and promising technology. By CRISPR technology, human gene can be introduced into the animal gene pool to develop chimera for human like cells/tissue. However, the long-term effects of gene editing in human are unknown. After revisiting the state-of-the-art publications in this discipline, it appears that the possibility of development to full-term chimeric/non-human animal by CRISPR technic for xenotransplantation is a future reality. Concern over the safety and ethical issues of gene modification remain for the xenotransplant recipient and the regulators. Countries like UK and the USA might find a leeway within which they would legally practice the research of development of the "non-human animal" to extract organs genetically compatible with the human body by hovering around the legal terminology. This article highlights the clinical, ethical, legal, and social issues of chimeric non-human animals for developing human-compatible organs. We have predicted how real and near the future is for gene modification and animal-human chimera formation for the purpose of xenotransplantation.

Key words: Chimera, CRISPR, ethics, non-human animal, xenotransplant, bioethics

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Introduction: Longevity can not be achieved without access to healthcare and the support of cutting-edge medical technologies. Organ transplant is the only option open to certain types of patients with particular health conditions. There are always more people waiting for a transplant than the available organs from donated sources [1]. According to US Department of Health and Human Services, over 100,000 Americans wait for organ transplants, and 6,000 of them pass away for waiting per year[1]. Science is exploring a new possibility to develop a chimera (fusion of more than one distinct set of genes of different animals) from the non-human animal for organ harvesting that is genetically compatible with human body[2]. CRISPR is the breakthrough technic for the creation of chimera introducing human particular organ gene into non-human animal that ultimately particular organ of nonhuman takes the recepient organ phanotype[3]. However, gene modification is not beyond the clinical, legal and ethical issues. After revisiting the literature, we can predicton how real and near the future is for the xenotransplantation. Law and the regulations regarding gene modification research in the selected countries' context were discussed in this article. We also have briefly analysed the clinical, legal and ethical issues involved in the xenotransplantation (organ transplant from the chimeric non-human animal source to human).

Methodology: This review article was prepared by extensive literature review of the published articles and books relating to the legal, clinical and ethical issues in "gene editing to form chimera" at the Department of Law, University of Dhaka, during the period of 2018 to 2022. PubMed, Google Scholar, Embase and HeinOnline were the preferred search engines. Relevant websites were also searched for the content on the subject matter. Chimera, CRISPR, ethics, non-human animal, and xenotransplant were the possible keywords to retrieval of the literature. This article investigated the law relating to research and the use of chimera in certain particular countries. The article search for the preparation of this writing includes publications between 2012 and 2023. The way forward, conclusion, and recommendations are the strength of this paper.

What is Chimera: Chimera is a single organism that is made up of cells of different embryonic origins and expresses two sets of phenotypes [4]. In antiquity, "chimera" was considered a monster-like creature composed of the body of a lion and head of a goat and the tail of a snake that was worshiped in Greek and Egyptian mythology[4]. Hermaphroditism (a person has both sex) is an example of a naturally occurring chimera[5]. Microchimerism (transfer of a small number of two sets of genetic material/cells/ tissue) also occurs during pregnancy (fetus to mother) [6], conjoined twins (sharing genetic material of both babies)[7], organ transplantation [8] and blood transfusion [9] etc. So "chimera" can be referred as the introduction of cells/ DNA of an individual into another organism to develop a cells/tissue/organ of an individual for human disease and treating several disorders.

CRISPR-Cas 9 technology of gene modification system cut a specific sequence of DNA through artificial restriction enzymes that alter specific sites of DNA in any organism by adding, activating, deleting or suppressing genes [10]. Researchers developed transgenic mice injecting ESC (embryonic stem cell) from a black mouse into a blastocyst from a white mouse and formed a bicolored (combination of black and white color) mouse chimera [11]. This system of genome modification can be used in plants and animals as well [10].

However, technological advancement now has opened up the development of interspecies hybrids chimera research for the procurement of human organs by CRISPR/Cas 9 intervention. Transfer of rat iPSC (induced pluripotent stem cell) into mouse blastocysts to produce mouse embryos with organs of rat has been successfully achieved [12]. In that way, human iPSC can be injected into blastocysts (107 cells stage embryo at 3 day) of genetically altered animals that give rise of autologous human organs [13]. Afterwards the chimeric (reaching required size) organ is harvested on the day of transplantation by

sacrificing the animal. With further development of technology, site-specific gene modification by Cas9 mRNA and sgRNAs is successful in one-cell fertilized eggs even [13]. CRISPR/Cas9 mRNA and sgRNAs open up iPSCs from a somatic cell bypassing animal germ line cell to produce own organs, which is a breakthrough invention and may reduce certain ethical crisis [14].

CRISPER/Cas 9 technic suppresses the immune response, as a consequence reduces the long-term need of immunosuppressive drugs after transplantation[15,16]. CRISPR kits are significantly cheaper, easier, and more efficient than others (for example, ZFNs or TALENs)[17].

The Legal Framework of Genome Editing, Development of Chimeric Non-Human Animal and Xenotransplantation in Select States: Gene editing Research is legal in the UK[18] with restricted regulatory framework[19]. Human Fertilization and Embryology Authority (HFEA) Act 1990 says "*gene editing or transfection can be investigated for research purpose*"[19]. *Embryo research for the creation of a human embryo in vitro, is allowed till 14th day after fertilization before the formation of the primitive streak [20].* Therefore, this law permits any type of germline research including human admixed embryo and chimeric embryo formation till the second week after fertilization [21].

The 1997 Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being sets the boundary for human genome modification. Article 13 of the Oviedo Convention states that the *human genome can be modified only for the "preventive, diagnostic or therapeutic purposes" and it is not allowed to introduce or do any modification of the genome of the next generation [22].* Only 29 countries have ratified the Oviedo Convention until 2022. However, the USA and UK are not signatories to this convention [23].

However, the Embryology Act of 2008 (UK), in its Section 4, prohibits to *create, handle and storage of human-animal admixture of embryo* [24]. *Human-animal embryo research can be done only by a license[24]*. Developing a non-human gene edited chimeric animal in a host animal to full term to derive an organ compatible with human body, does not seem to be legal under the current law of UK. However, Currently, Home Office of UK in January 2016 stipulated new regulation that research involving the use of human material in animals requires authorization of the HFEA and research body and Animals in Science Committee [25].

On the other hand, the law of the United States stipulates gene editing in human embryos without any legislative restriction before 2005[26]. National Institute of Health (NIH) Revitalization Act in 1993 allowed research involving human embryos and embryo research was funded by NIH [27]. However, ten years later, in 2005 the U.S. National Research Council and the Institute of Medicine recommended limits on research of human-nonhuman cells including animal-human chimeras[4]. Moreover, current, Human-Animal Chimera Prohibition Act of 2021 contains rules on: a) *create, attempt to create human-animal chimera, b) transfer or attempt to transfer a human embryo into a nonhuman womb, c) transfer or attempt to transfer a nonhuman embryo into a human womb* [28]. A clinical trial of gene therapy is currently highly regulated by the FDA's (US Food and Drug Administration) [29] and also xenotransplantation research, of live cells, tissues, or organs from a nonhuman animal source into a human recipient are regulated by Cellular, Tissue and Gene Therapies Advisory Committee of the FDA [30, 31]. Admixture of human and animal research are not eligible for NIH funding [32]. Nevertheless, 83% of respondents can personally accept research on human-animal chimeric embryos [33].

However, French and German law stipulates restrictions to develop chimeric human embryo. Both countries are not clear about the law of human-animal chimera formation[4]. Japan allows the human-animal chimeric development until the preimplantation stage (fourteen days of post-fertilization) but

prohibited to chimera transfer into an animal uterus [4].

Ethical, Legal, Clinical, and Societal Issues Concerning the Chimera: CRISPR gene modification is a versatile method. However, it is a new system of biomedical tools that has raised clinical, legal, ethical, and societal concerns. A multidisciplinary intellectual approach is required to address the legal, moral-ethical and social implications of gene modification having biomedical applications [5].

Legal Issue: There is a lack of legal consensus on whether this technology should be controlled by individuals or requires international regulation [34]. Intellectual property rights on CRISPR (most likely patent) may limit the access to healthcare for all [16]. Research in human-animal chimera and therapeutic application need tough Government regulation [16].

Ethical issues Concerning the Chimeras: Certain ethical controversies surround genetic modification research (where embryonic stem cells accrue by the destruction of a human embryo). Destruction of the embryo is not permitted in some religions (including Catholics and Hindus who consider it immoral) [35]. They consider life begins at the time of fertilization. The moral status of the conception is contemplated as human [35]. Autonomy and vulnerability are the legal and ethical concerns regarding the research with chimera [32].

In human-animal chimeric research, pigs are usually used as hosts for organs because the organ size and metabolism of the pigs are almost compatible with humans. However, it raises ethical concerns over the welfare of the animals [32]. Moreover, CRISPR /Cas9 technic with the human iPSC encompasses questions: would it develop a human-like intelligent brain (in the host), demonstrate human-like language, the ability to learn and solve complex problems and have human emotions? Can it be justified to destroy them simply because they are not human? [36]. Are they created just to satisfy the human quest for longevity? How can we anticipate the risks-benefits ratio?

Clinical Issues with Chimera: CRISPR/Cas9 method includes risk since it requires different DNA arrangements to changes. Moreover, CRISPR causes 50% more off-target activity-induced mutations than the desired mutation, which could lead to genomic instability and disrupt functionality [37]. However, the risk of exchanging off-target mutants within the same species may increase the heritable mutant quality. Off-target mutant gene may exchange to other species and has the chance to transform negative characteristics to generation [10]. Patients may suffer the psychological risk of sorrow, anxiety, and distress in life for the plausibility of hereditary illness in their child.

However, animal-human chimeric organs for transplantation may pose serious risks because of the expression of animal proteins that could elicit serious immunological reactions [38]. CRISPR human-animal technology may entail deliberate risk of injury or death of cell that may cause harm to human safety and dignity [39]. Considering the unpredicted applications, a careful examination of its moral and societal suggestions is required [38].

Another important clinical concern is that the fetus is not small adult in development and function[40]. Digestion, metabolism, and protein expression of the embryo is quite different than in adults. Therefore, fetal development by gene modification cannot be accomplished for an adult's disease[40].

Societal Issues: Social inequity and injustice is the concern with high-tech animal-human chimera [41]. CRISPR technic is high-cost medical treatment. All costs for implant and post implant medical care will be borne by the recipient [42]. Only the rich and famous will be able to afford it, which increase the gap between rich and poor who really need the technology medically [42]. Furthermore, there are concerns about the CRISPR technology that patients may not live long after spending high cost of the therapy [38]. Germline and/or somatic cells may intend to order for designing a particular phenotype[42]. And there may be a black market for the organ transplants [43].

Conclusion: From the above literature, it can be concluded that moral and legal doctrine emerge that embryos do not have the moral status as human persons till fourteen days after fertilization. This provides the moral status less than human as it is still in cellular entity. This paves the way for genetic editing research. The development of iPSCs from a somatic cell by CRISPR process is a breakthrough research that bypasses animal germ line cells and is still capable to produce own organs. This is a versatile research and it may change the definition of chimera. Research is still legally possible for the development of organs genetically compatible with humans in certain countries. By this technic an embryo may not be required to be destroyed for research. Gene editing tech of iPSC may provide own organ for transplant surgery by reducing transplant truism and black market. Possibility of the xenotransplantation is a distant future reality. Strict law and regulation are required for the biomedical application of this new technology. Moreover, this CRISPR/cas9 procedure may have the possibility of long-term adverse side effects. The scientific rigor of non-human-human chimera is necessary before the clinical application. Finally, the introduction of xenotransplantation products should be considered only for medically indicated specific conditions of patients. The age and overall health conditions of the recipient may be taken into consideration.

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