An Overview of Clinical Xenotransplantation Regulatory Issues

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ABSTRACT

Living organ, tissue, or cell transplantation from one species to another is known to as xenotransplantation. The history of xenotransplantation is just as ancient as that of allogeneic transplantation. Early attempts were attempted when it was uncertain exactly, on an immunologic level, causes organ rejection. With the emergence of potent immunosuppressive medicines and concurrent advancements in the field of genetic engineering, a new perspective on the role of xenotransplantation as a tactic to resolve the disparity between the number of applicants on the waitlist and the available organs has developed. Although a xenotransplantation clinical trial involving human subjects appears to be theoretically viable, it requires a stringent regulatory framework on both a national and international level to ensure both the individuals' and the public's safety. Several scientists in the United States urged the FDA to prohibit cross-species transplantation research until ethical concerns and health risks are addressed at the public conference on xenotransplantation that was held in January 1998. Clinical studies that are being conducted cautiously and with precision were approved by the FDA as suitable. ARMBA and the roles of the relevant governmental organisations and healthcare institutions are the focus of the present rules regulating the conduct of xenotransplantation clinical trials in Korea. In accordance with the standards of the international guidelines, Korea is prepared to perform a clinical experiment involving xenotransplantation on humans. In accordance with the ARMBA and other relevant laws and regulations, the appropriate governmental authorities would work together to control the xenotransplant clinical study.

Keywords: Xenotransplantation; Xenograft, Solid organ transplantation

INTRODUCTION

End-stage organ failure can be successfully treated by transplantation. However, an obstacle for clinical transplantation is the disparity between supply and demand for human organs. More than 113,000 individuals were on the transplant waiting list as of January 2019, according to the US Government Information on Organ Donation and Transplantation, whereas only 36,528 operations were conducted in 2018. There are over 300,000 people on the waiting list for organs in China, but only 16,000 are made available each year. Xenotransplantation could be a different approach to this genuine issue (Fig 1).

Any technique that includes the transplantation, implantation, or infusion into a human recipient of either [1]:

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- Living tissues, cells, or organs derived from non-human animals.

- Bodily fluids, cells, tissues, or organs from living non-human animals that have had in ex vivo contact with human cells, tissues, as well as organs is how the World Health Organization (WHO) characterises xenotransplantation.

Because it brings up all the complex bioethical concerns in one scenario, xenotransplantation is a fascinating topic in applied ethics. Informed participation, clinical trials, animal experimentation, questions of personal identification, transgenic animals, and even public health concerns are all covered by this.

The endeavour to use living biological components from non-human animals in humans for therapeutic benefits is known as xenotransplantation. The US Public Health Service's definition of xenotransplantation is more precise: it is the transplant, implantation, or infusion of live nonhuman animal cells, tissues, or organs into a human recipient, as well as the use of human body fluids, cell lines, tissue samples, or organs that have mixed ex vivo with live nonhuman animal cells, tissues, or organs. The potential of xenotransplantation could appear remote. It is now more likely than ever for infertile couples to become pregnant using in vitro fertilisation, a process that involves removing the eggs and sperm from the intended parents, fertilising the eggs in a lab, growing the fertilised eggs to a multicellular stage over three to five days, and implanting the eggs into the mother's uterus. In the 1990s, it was standard practise in laboratories to use a cell line of nonhuman origin as the substrate to encourage the development of a fertilised egg into the multicellular stage.

According to the US Public Health Service definition, the multicellular stage fertilisation product that was transplanted into the mother's uterus and eventually gave rise to the child was a xenotransplantation product. Additionally, hundreds of patients have undergone treatment with experimental xenotransplantation products intended to, among other things, improve functions in patients with Parkinson's disease after implantation of porcine neurological cells, lessen the need for insulin in diabetics, or extend the lives of hepatic failure patients until a liver transplant is feasible (hemoperfusion through a porcine liver or hepatocytes) [2].

The issue of xenozoonoses is raised by baboon-human xenotransplantation. Herpesviruses and retroviruses are the most dangerous organisms, however they may be detected and eradicated from the donor pool. Toxoplasma gondii, Mycobacterium tuberculosis, and encephalomyocarditis virus are among the others. Filoviruses (Marburg and Ebola), monkey pox, and Simian hemorrhagic fever virus are less likely to be discovered in animals bred in confinement in the United States. Lymphocytic choriomeningitis virus, gastrointestinal parasites, and GI bacterial infections are examples of organisms that are unlikely to be transferred with an organ donation but should be checked for.

The danger of xenozoonoses is most likely limited to the receiver of xenogeneic tissue. Nonetheless, the potential for xenozoonotic transmission across the human population must be considered and anticipated as a public health risk. Controlling the donor animal vendor source and the individual donor animal by applying stated screening tests and stringent sterile procedures during organ harvesting and donor autopsy for tissue and blood can decrease, if not eliminate, the risk for identified zoonotic diseases. The danger of unidentified pathogens exists but is poorly characterised.

Surveillance for disease transmission among health care professionals must be undertaken by monitoring for unexpected or unexplained adverse health outcomes. It is difficult to monitor for the unknown; consequently, monitoring should involve informing the main investigator's office of any unexplained sickness among exposed health care workers, as well as conducting telephone interviews with these employees every 6 months [3].

Organ	Waiting List	Transplant
Kidney	108,238	14,879
Liver	15,275	5,651
Pancreas	1,040	187
Heart	4,198	2,331
Lung	1,552	1,694
Heart / Lung	49	12

Figure 1: Global overview of organ and tissue transplantation.

Advancement of Porcine to Human Organ Xenotransplantation

- The global market for organ and tissue transplantation items and technologies was $59,6 billion in 2014, with a projected increase to $90 billion by 2020.
- There is a significant lack of acceptable human organs for clinical transplantation, which is driving an increase in demand for synthetic and/or xenogeneic organs.
- Intrexon's integrated technologies and patented platforms, including its genetically diversified lone star Yucatan miniswine families, provide end-to-end solutions for cell and orange engineering for xenotransplantation [4] (Fig 2).

MATERIALS AND METHODS

Search Strategy

This paper is exclusively a review article so all the information has been collected from the secondary sources:

- Books and journals
- Proceedings, articles, Reports
- Internet browsing
- Suggestions and valuable information
- Compiled and arranged chronologically

MAIN TEXT

Types of Xenotransplantation

Blood Transfusion

- Animal blood was used in the earliest human blood transfusions. In fact, human blood transfusion and xenotransplantation both originated from xenotransfusion. The ground-breaking work in this field is described in this review.
- Henri Louis Hebert Mont-mort, a scientist who lived from around 1600 until 1679 founded in Paris, which subsequently evolved into the French Academy of Sciences, was where the concept of blood transfusions was initially conceived.
- During his tenure as King Louis XIV's physician from 1635 to 1704, the first transfusion of animal blood into a human was by a Frenchman by the name of Jean-Baptiste Denis (Fig 3). On March 3, 1667, Denis transfused blood between two dogs after being inspired by Lower's investiga-

tions. The blood from three transfusions of calves was then administered into three dogs.

- During his second xenotransfusion, which took place in June 1667 (precise date uncertain), Denis paid a 45-year-old healthy guy to take part. Denis took 300 ml, or ten ounces, of the injected the same volume of arterial blood from a lamb along with the subject's blood [5].

- On June 24, 1667, Baron Bonde, a young Swedish noble person who became ill in Paris, received the third transfusion. He was so ill that four different doctors had to bleed him. The patient was virtually comatose, unable to talk, and throwing up when Denis and Emmerez arrived. He drew six ounces of blood from a cow and started talking. He felt better during the following 24 hours, but then his illness relapsed. The patient continued to exhibit faint indications of improvement as Denis started a new transfusion, but soon passed away [6].

Skin Xenotransplantation

Skin grafts between different animal species and people were common in the 19th century. They were either pedicle or free grafts. Pedicle grafts were challenging since the donor, such as a sheep, had to stay motionless while being strapped to the patient for many days, during which the recipient was supposed to vascularize the graft. The graft may be severed from the donor if this happened. Although several "successes" were claimed, it's quite likely that none of these grafts were effective in any way. Although there was a propensity to use animal species without these accessories, many of the animals chosen as donors—including sheep, rabbits, dogs, cats, rats, chickens, and pigeons—had hair, feathers, or fur growing from the skin. As they occasionally came "skinned alive," frog skin would have made the greatest transplant. When used to cover skin ulcers, it's likely that some of these grafts were "successful" in the view that they offered defence, if only for a few days, while the ulcer beneath them healed. But it's likely that none of the grafts turned out to be long-lasting [7].

Corneal Xenotransplantation

A tried-and-true method for treating corneal blindness is corneal allotransplantation. However, the scarcity of human donors necessitates the investigation of other therapies such corneal xenotransplantation (using pigs as donors, for example) and bioengineered corneas. Great strides have been achieved in the creation of genetically modified pigs, efficient immunosuppressive regimens, and the formation of standards for the conduct of clinical trials since the first attempt at corneal xenotransplantation using a donor pig cornea in 1844. We emphasise challenges to corneal xenotransplantation that include immunological and physio-anatomical, recent advancements in investigations using non-human primates, and regulatory criteria for conducting clinical trials for corneal xenotransplantation [8].

Xenotransplantation of Cells Rejuvenation

A few years later, Serge Voronoff, a Russian immigrant who lived and worked in Paris, developed the concept of transplanting cells that produced a hormone that the recipient lacked. This is yet another tale of a forward-thinking scientist with vision. He was thinking about what we are already doing, this involves giving people with type 1 diabetes transplants of human pancreatic islets, which create insulin. There is a lot of interest in utilising pig islets for this reason since there are only a certain number of human pancreases available each year.

But Voronoff's major focus was on slowing down the ageing process in older men who had lost their "zest for life." He performed a substantial number of transplants of baboon or chimpanzee testicles into male human patients. His method involved cutting the animal testicle into slices and inserting the pieces into the testicles of the recipients. There were several hundreds of these surgeries conducted as the method gained popularity on both sides of the Atlantic. It is unlikely that any of them had any positive effects at all, save from psychological ones, although there have been tales of extraordinary "rejuvenation" in men who

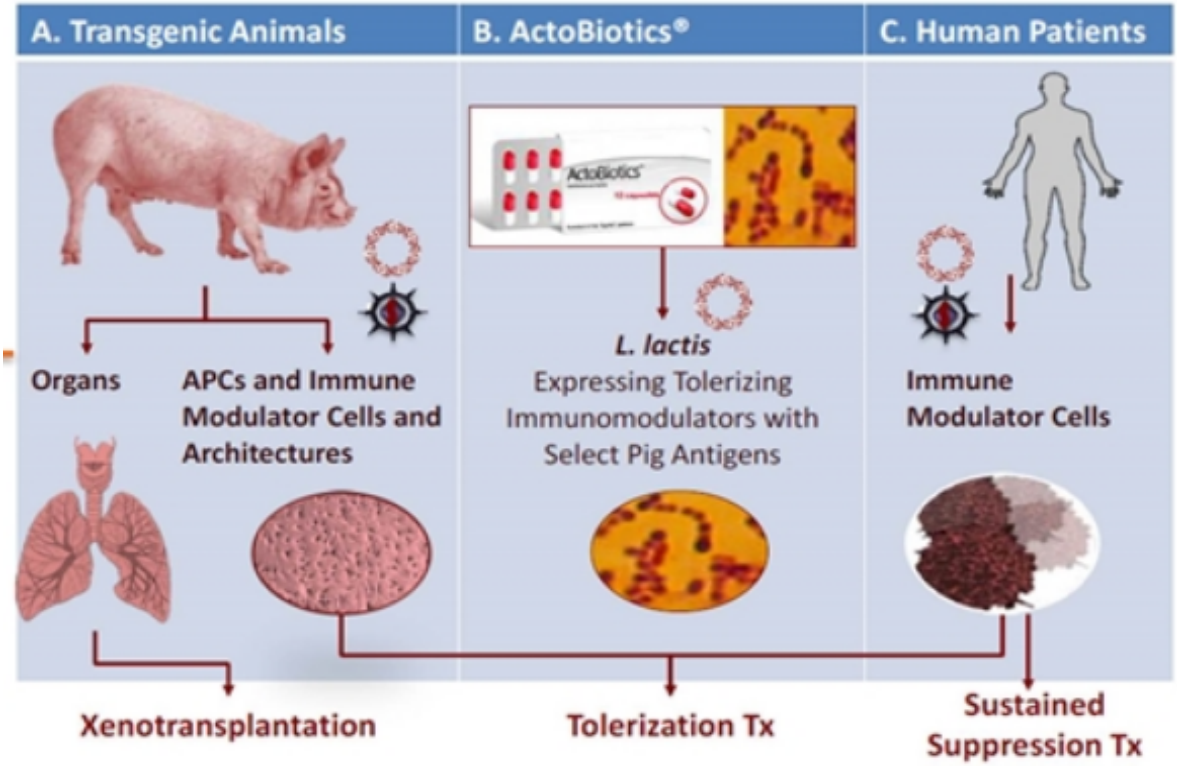

Figure 2: Process of Xenotransplantation.

have undergone surgery and reported having more energy. Surprisingly, it seems like there weren't many complaints of difficulties.

A far less scientific physician named John Brinkley, who mostly practised in Kansas and Texas, continued on the practise in the United States of glandular tissue transplantation to create hormones beneficial to the recipient. He chose the goat as a donor after being persuaded of its sexual potential by a neighbouring farmer [9].

Kidney Xenotransplantation

There are over 100,000 individuals in the United States waiting for kidney transplants, and there is a huge need internationally. Xenotransplantation is a potential answer to the continuous lack of deceased and active human donors, which involves transplanting kidneys from genetically modified pigs. The following genetic deviations are possible [10]:

(i) The introduction of human transgenes that provide defence against the inflammatory, coagulation, or complement reactions in humans; or

(ii) Pig genes that control the production of antigens that primates (human or nonhuman) normally "preform" antibodies to bind to and begin complement-mediated destruction are knocked out.

Pig kidney transplant survival in nonhuman primates rose from 23 days to more than 10 months between 1989 and 2015. There do not seem to be any physiological distinctions between pigs and monkeys' renal function that are clinically significant. Due to the pigs' housing in a bio secure environment, the chance of introducing an exogenous, potentially harmful bacterium will be lower than after allo-transplantation. Although technologies are now available to potentially exclude swine endogenous retroviruses from the pig, their threat is still considered to be minimal. Xenotransplantation should only be used for

Figure 3: A lamb-to-man blood transfusion experiment (1705).

"people with significant or life-threatening illnesses who do not have appropriately safe and effective alternative therapy," according to the US Food and Drug Administration. These might include those with [11].

(i) An extensive sensitivity to human leukocyte antigens.

(ii) Fast relapse of original illness in previous allografts.

Heart Xenotransplantation

James Hardy, who conducted the first human lung allotransplant in 1963, was pleased to know that some of the patients of chimp kidney transplants were doing well. Hardy had six chimps on the way as possible "donors" in case he was unable to find a deceased human. He was determined to execute the first clinical heart transplant in 1964 and had six chimpanzees on the way. His physique was severely affected by athermanous vascular disease. This necessitated amputating both of his legs, and the fact that he was semi-comatose at the time

Device	Processing
Pericardial valves (bovine)	-Sheets of bovine pericardium mounted inside or outside a supporting stent. -Sterilization: chemical (glutaraldehyde), radiation (gamma, microwave)[30]
Viscera gut sutures (bovine, ovine intestines or from bovine tendon)	-Sterilized with fluid containing ethylene oxide, isopropyl alcohol, distilled water[31,32]
Dental implants (bovine bone)	
Collagen sheets/dressings/shields (equine, bovine, porcine)	-Cross-linking methods: chemicals (glutaraldehyde, isocyanates, sugars, carbodiimides), mechanical (heat) and/or radiation (UV, gamma) in the presence of activators. -Sterilization methods: chemicals (ethylene oxide or glutaraldehyde), radiation[33]
Collagen corneal shield (porcine sclera or bovine dermis)	-Corneal shield crosslinked with UV, supplied in dehydrated form requiring rehydration prior to use. Made of type I and some type III collagen[34]
Bioprosthetic valves (porcine)	-3 porcine aortic valve leaflets cross-linked with glutaraldehyde and mounted on a metallic or polymer supporting stent. Now commonly treated with anti-calcification agents as well to improve lifespan of device. Intact porcine aortic valve preserved in low-concentration glutaraldehyde solution - reduces antigenicity and stabilizes tissue against proteolytic degradation.[35]

Figure 4: Processing tissue examples.

of the transplant; he had a patient who was less than perfect and who today would not be eligible for a heart transplant. Hardy was compelled to perform a chimpanzee heart transplant, nonetheless, because the patient was in danger of passing away. The heart failed after a few hours because it was too little to support the circulation.

The heart xenotransplantation received a negative reception from the public and medical community in contrast to how they felt about the attempted lung allo-transplantation, which discouraged Hardy and his colleagues from continuing their attempts.

Barnard and his colleagues then invented the process of cardiac allotransplantation in 1967, and they later performed two heterotopic cardiac xenotransplantation, utilising chimps and baboons as 'donors' [12].

Regulations for Clinical Xenotransplantation in USA

Cross-species transplantation, or xenotransplantation, has garnered attention as a solution to the continuous, catastrophic scarcity of organs and cells from deceased human donors. The pig is seen to be the most promising source of organs at this time. Considerable progress has been made in the lab to increase cell and organ xenograft survival in a range of pig-to-nonhuman primate systems since the US Food and Drug Administration finished a detailed review of xenotransplantation in 2003. These technologies now offer the best clinical outcome prediction models. In nonhuman primates, the survival of transplanted hearts, kidneys, and islets is now measured in months or even years. After a thorough investigation, it was discovered that the possible risks of xenotransplantation, including the transmission of an infective microorganism,

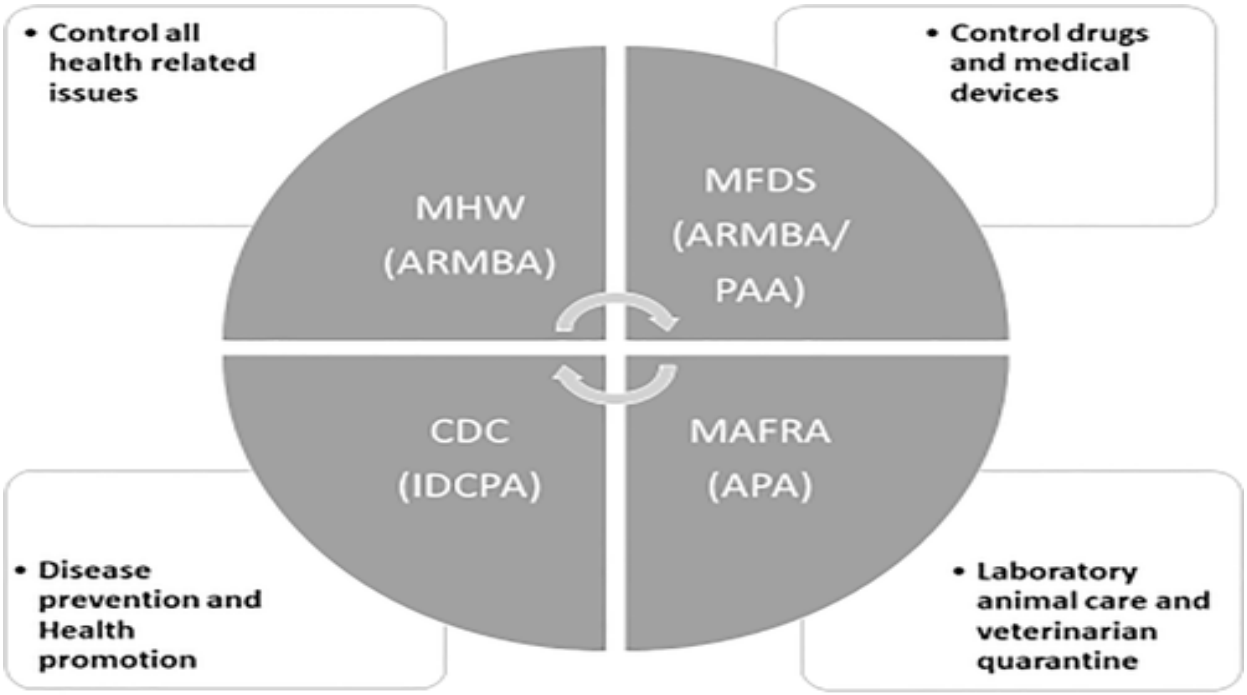

Figure 5: Korea's general xenotransplantation regulating bodies.

which were illustrated in the 2003 Food and Drug Administration guidelines and subsequent World Health Organization consensus documents, were either less likely than previously believed or pretty doable through donor selection or recipient management strategies. It is required that national regulatory authorities throughout the world revaluate present xenotransplantation guidelines and rules to make it easier to organise and conducted clinical studies of human cell xenotransplantation that are safe and informative as well as and supported by preclinical evidence.

Since the US Food and Drug Administration (FDA) completed a thorough review of xenotransplantation in 2003, significant advancements have been made in the experimental setting to increase cell and organ xenograft survival in a number of pig-to-nonhuman primate systems, which present the best models currently available to predict clinical outcomes. Waiting patients are passing away without obtaining a donor organ because the rising number of human deceased clinical transplantation of donor organs has not been able to keep up with the rising candidate backlog [13].

Risks

Potential risks associated with xenotransplantation, such as the transmission of an infectious microorganism, were highlighted in the World Health Organization (WHO) consensus documents that accompanied the FDA guidance from 2003. However, extensive research has shown that these risks may either be easier to control by donor selection or person who received management measures, or they may be less likely than previously believed. Researchers think that since the FDA and other national (UKXIRA, Med Safe, etc.) and international (WHO) regulatory authorities last completed their thorough evaluations in the first half of the previous decade, the risk-benefit ratio related to pig-to-human organ and tissue transplantation has significantly changed. Scientists recommend that national regulatory authorities all over the world revaluate their standards and laws governing xenotransplantation in order to better facilitate and justified by the clinical trials of cell and organ xenotransplantation that are safe and instruc-

Table 1: Overview of regulatory Aspects in porcine xenotransplantation products.

Subject	Aspects	Example – PERV Safety
Source herd	• Facility • Close herd • Accommodation • Monitoring infectious pathogens • Food • GMP compliance	• Document • Existence of PERV (subtypes) • In vitro transmission to human cells
Source animal	• Health check, including infectious pathogens • Quarantine and release transport • Organ harvest and animal disposal • Records and sample storage	• In case of interanimal variability, repeat studies as documents for source herd • Archive records and samples
Product manufacturing	• Process validation • Testing infectious pathogens • Product characterization • Release characterization • Release testing	In case of inter-organ variability, document existence of PERV (subtypes)
Patient	• Clinical protocol • Patient selection • Informed consent • Transplant clinics • Follow up monitoring • Record, sample storage	• Monitor recipient for in vivo PERV transmission • Archive records and samples

tive, as well as preclinical data planning and execution [14].

Preclinical Progress

Xenotransplantation has advanced, thanks to a methodical investigation of the technical obstacles. Each challenge has been addressed, either by genetically altering the pig used as an organ donor or by creating and utilising brand-new immunosuppressive and anti-inflammatory medications.

For more than two years, genetically modified pig heart transplants in baboons were successful; they only stopped working when all immunosuppressive medication was stopped. Baboons and monkeys have thrived on genetically engineered pig kidneys during a period of time that exceeds six months, and in one instance, a year. Using both genetically engineered and wild-type pig islets, insulin-independent normoglycemia has been maintained in diabetic monkeys for durations longer than a year and, in one case, for more than three years. For more than a year, mesencephalic pig cell genetic engineering has been employed to lessen the outward signs of a Parkinson-like sickness in monkeys. Graft survival has significantly increased, even in the difficult liver transplantation from a pig to a baboon paradigm, reaching more than one month in two recent cases. Consensus standards meant to prompt consideration of clinical trials are quickly approaching for preclinical outcomes. Indeed, encapsulated pig islet transplantation and decellularized pig corneal transplantation are now undergoing clinical studies, and the patient selection for the earliest It is being considered to conduct clinical studies on xenotransplanting solid organs from pigs [15] (Fig 4)

Porcine Endogenous Retroviruses: Progress (PERV)

Recent experience suggests that the risk of (PERV) infection in human recipients may be lower than previously believed. Based on the molecular sequencing of PERV, genetic screening and statistical diagnostics for circulating PERV have been developed. These developments have made it possible to design

testing processes for source animals, organ donors, and human recipients. Despite the prospect that chronic micro-chimerism in xenograft recipients may enhance the chance of delayed donor-derived infection, there has been no evidence of transfer to human xenograft recipients or in preclinical pig-to-primate trials. Wild-type skin transplant recipients who had suffered burns did not exhibit any symptoms of infection. Market-available antiviral drugs also combat PERV. Despite the fact that PERV receptors exist, a variety of internal processes seem to further limit PERV's ability to infect human cells. Other approaches, such choosing pigs with fewer PERV loci, have been proposed. These methods were used in a clinical trial in New Zealand without conclusive evidence of PERV transmission, even though this study did not include immunosuppressed patients. The same result was reached after patients in a second clinical investigation in Argentina got transplantation of pig islets in capsule form. The spread of PERV should be restricted or stopped entirely using more recent molecular approaches, instance such as the development of pigs with the PERV gene eliminated utilising CRISPR-Cas9 technology or short interfering RNA technology [16].

Korean Research Group (XRC) and Xenotransplantation Clinical Trial

The Changsha Communiqué's requirements for the scientific prerequisites for the xenotransplantation clinical trial involving humans were satisfied by the XRC's fairly effective findings in the preclinical study with non-human primates. Since 2012, Korean researchers have begun putting together the essential steps and guidelines for clinical studies with human volunteers using swine pancreatic islets and cornea. The general protocols and procedures used in Clinical research for biologics or cell treatments aid in overcoming the regulatory and bioethical difficulties associated with xenotransplantation because there is no established regulatory framework for it in Korea. The regulating authorities are the Ministry of Food and Drug Safety and the Ministry of Health and Welfare and they held off on allowing xenotransplantation clinical studies primarily for ethical and safety concerns. Their reluctance to approve the clinical trial was due in part to the absence of a relevant international precedent, specifically the clinical experiment involving systemic and regulated xenotransplantation of humans. In order to assess the strategy, The IXA Ethics Committee was engaged by the XRC regarding the design, protocol, and clinical research in 2018 in Korea. The proposal was examined by the XA IXA Ethics Committee, which functioned as the spokespersons for the IXA and TTS and coordinated international xenotransplantation regulations with WHO. The committee came to the opinion that xenotransplantation is not currently subject to "effective regulation by the government" in Korea. As a result, the committee

(a) Vehemently requested that the Korean government pass the "The Advanced Regenerative Medicine and Bio Pharmacology Act (ARMBA)" or revise the "Infectious Disease Control and Prevention Act (IDCPA)" to explicitly include xenotransplantation practises in order to provide a clear regulatory framework and regulate the clinical xenotransplantation experiments being conducted in Korea;

(b) Urged to examine and, if allowed, supervise any upcoming xenotransplantation experiments conducted in Korea as well as clinical research, the Korean government is required to establish a systematic regulatory process. This method should be handled by the Korean Ministry of Health and Welfare, the Ministry of Food and Drug Safety, or a combination of the skills of both organisations. Fortunately, the National Assembly eventually approved the ARMBA in 2019, and it will take effect in August of that same year.

After so many turns and turns, the act finally stipulates particular items for xenotransplantation, which is regarded, referred to as an example of "advanced regenerative medicine." After establishing a strong legal and regulatory framework, Korea can conduct a clinical trial for xenotransplantation [17].

Overview of General Xenotransplantation Regulations in Korea

In addition to the ARMBA, a number of other laws and rules also apply to clinical trials in Korea, innovative treatments and medications (IND) primarily, the Pharmaceutical Affairs Act. Overarching legislation in this sector according to the Prime Minister's Ordinance, the statute mandates that each maker of new medications acquire marketing permission from the Food and Drug Safety Minister (MFDS). The manufacturer is required by the Prime Minister's Ordinance to provide the Minister of FDS with the documentation attesting to the drug's efficacy and safety, including the findings of any clinical trials. A clinical study plan must be prepared and approved by the Minister of FDS, according to the PAA, which also mandates that manufacturer undertake clinical trials. The Prime Minister's Ordinance details the particular regulations governing clinical trials for INDs in addition to giving for clinical trials, "Korea Good Clinical Practice (KGCP)," as it is known. Clinical trials must be conducted in Korea in accordance with the "KGCP" rules as well as global norms like the Declaration of Helsinki and the CIOMS guideline. The Medical Device Act's same regulatory structure should be followed in clinical trials for medical devices (MDA). Acellular xenogeneic products, such as acellular porcine cornea, might be categorised as "medical devices" and be subject to MDA regulation [18].

Clinical studies for academic or other non-commercial purposes as well as those of pharmaceutical products requiring marketing authorisation are governed by the PAA. Additionally, the Bioethics and Safety Act (BSA), passed in 2005 and completely updated in 2012, regulates all research involving human subjects, including clinical trials. The BSA mandates IRB review and informed consent for all human subject research, including that conducted in the fields of behavioural sciences and biomedicine (with a few exceptions, of course). Therefore, clinical studies conducted for academic or other non-commercial objectives must also adhere to BSA. However, because xenotransplantation is not covered in either PAA or BSA, the issue is not adequately handled by the acts.

After it was approved on August 27, 2019, dependable the Advanced Regenerative Medicine and Biopharmaceutical Act provide regulations for xenotransplantation clinical trials in Korea (ARMBA). In addition to establishing the overall framework for the clinical inquiry into xenotransplantation, the ARMBA also regulates the experiment with other crucial acts. Although ARMBA has been established, its enforcement decrees have not yet been established; therefore, the clinical trials for xenotransplantation are now not administered by ARMBA, but rather, on an individual basis, by PAA. For instance, a cell therapy trial governs the clinical investigation for corneal xenotransplantation. There are many variations in xenotransplantation and cell therapy, which complicates the IND procedure. However, via collaboration with MFDS and academics, the development of high-quality testing protocols and non-clinical research standards has been on-going. The first IND for corneal xenotransplantation is anticipated to be approved early in 2020. The ARMBA and the Infectious Disease Control and Prevention Act would provide the essential protections to stop the emergence of new illnesses when used together. The Animal Protection Act would oversee the subject of animal protection and proper treatment (APA). Numerous governmental organisations, including Participants in the xenotransplantation clinical study include the NBC, the centres for Disease Control (CDC), the Ministry of Agriculture, Food, and Rural Affairs, the Ministry of Health and Welfare (MHW), and the Ministry of Food and Drug Safety (MFDS) (MAFRA) [19].

The key governing authorities for xenotransplantation in Korea are briefly summarized in Fig 5.

Xenotransplantation Clinical Trials Regulatory Requirements Geneva, Switzerland

The Geneva Consultation, also known as the Second WHO International Consultation on Regulatory Requirements for Xenotransplan-

tation Clinical Trials, was held from October 17–19, 2011, at the WHO's Geneva headquarters. Luc Noel greeted the participants, representatives of health regulatory organisations, and experts in the science, legislation, and ethics of xenotransplantation from all 14 Member States of the WHO. He expressed his appreciation for the financial support provided to make the consultation possible, by the International Xenotransplantation Association (IXA) and The Transplantation Society (TTS). Emanuele Cozzi, president of the International Xenotransplantation Association, emphasised the need of consensus among medical experts, authorities, and experts on the many safety standards for the practical practise of xenotransplantation as shown in Changsha. Although more conventional sources of funding for normative efforts are envisaged in the future, the help provided by TTS and IXA is justified by the need for consistent updates [20].

Current Xenotransplantation Procedures and Preliminary Scientific Development

The state of xenotransplantation today preclinical xenotransplantation efforts has revealed substantial advancements. Using a range of immunosuppressive or immune-isolation techniques, numerous groups have shown diabetic baboons and monkeys to have swine C-peptide while maintaining blood glucose normalisation. Following unilateral implantation of genetically altered pig neural cells, immunosuppressed primates usually show well-documented improvement in Parkinsonian symptoms. Using different immunosuppressive procedures that might be useful Anti-Non-Gal antibodies can be stopped or, in certain cases, greatly delayed. It is widely recognised that residual physiological barriers contribute to platelet adhesion and coagulation cascade activation by pig xenografts in primates; hence a number of potential preventative measures will shortly be investigated. The Changsha candidate pig-to-human xenograft applications that seem most likely to enter the clinic first, assuming the Changsha criteria for preclinical evidence of efficacy and safety are met, are ex vivo liver perfusion (as a bridge to transplant or recovery) and islet and neural cell transplantation (Table 1).

Regulated Clinical Studies for Xenotransplantation

In New Zealand, there has been one authorised clinical investigation employing intraperitoneal alginate-encapsulated porcine islets in individuals without immunosuppression. 14 recipients of encapsulated islets have not yet been associated with any safety concerns. The regulatory clearance and oversight framework in New Zealand is regarded as being thorough. Interim corporate reports that have not undergone peer review have not yet shown convincing proof of effectiveness. There are currently no known ongoing controlled xenotransplantation experiments [21].

Porcine Endogenous Retroviruses: Progress (PERV)

The potential for human cells to become infected by the pig endogenous retrovirus (PERV) and spread to the recipient's close contacts or the public, infecting a human recipient of a swine xenograft, raised concerns. There is currently a substantial amount of new preliminary evidence that [22]:

- Only exceptional circumstances lead to PERV infection of human cells, and PERV seems to need permissive cell types to spread.
- In spite of rigorous recipient immunosuppression, both non-human primates and people who have received pig organs or cells in preclinical settings have not demonstrated productive PERV infection. The PERV phenotypes of the source pigs used in this research are not known.
- Methods for PERV diagnosis in recipients of organ or cell xenografts have been established, and some of these methods, such as serologic and molecular testing, can help identify PERV replication.
- There are also preventative measures, such as antiviral medications, which are anticipated to be effective in averting or treating potential PERV infection situations. Should productive infection arise, these tests can assist control risk for individuals,

close contacts, and the public.

- In theory, it is better if PERV C or its isotype cannot be found in a pig used as a source animal for xenografts. It is required to monitor both donors and recipients for PERV, with the precise technique depending on the pig's PERV status. The FDA's current recommendations do not specifically prohibit PERV C+ pig source animals, however close observation is required for a favourable outcome.

CONCLUSION

Basic research in the area of xenotransplantation has advanced quickly, and clinical tests for certain xenotransplantation applications are now being conducted. The use of xenotransplantation in the treatment of human illnesses may also be beneficial. The fact that infectious diseases may spread from animals to people, it is well recognised that some organisms may be dangerous to one species while being innocuous to another. Furthermore, it is known that different environmental factors may affect an infectious agent's pathogenicity, and that some infections, like the human immunodeficiency virus, can have long-lasting effects. Given that xenotransplantation entails the direct implantation of potentially pathogenic cells, tissues, or organs into people, there is every reason to think that the prospect of infectious agent transfer from animal transplant recipients to human recipients is genuine. Some of these infectious agents may not even be known to exist at this point. If the disease spreads from the receiver, it must be taken seriously as a hazard to caregivers, family members, and the public.

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