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Review

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Xenotransplantation: past, present, and future directions

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Abstract

Xenotransplantation, in its broadest sense, is the transplantation, implantation, or infusion of cells, tissues, or organs from one species to another. While there is a high demand for human tissues, cells, and organs for use in clinical transplantation, they are often in short supply. Recent scientific and biotechnological advancements, coupled with the scarcity of human allografts, have led to renewed interest in developing exploratory treatment strategies that use xenotransplantation products in human recipients. However, despite its potential benefits, the use of xenotransplantation is still limited due to various considerations, as discussed in this review of the past, present, and future directions of xenotransplantation. One of the key ethical concerns surrounding xenotransplantation is the potential impact on the animals from which the cells, tissues, or organs are obtained. As with genetic modification to fix genetic defects or prevent disease, the ideal outcome for these animals is that they will be better off as a result of the change. However, unless there are major changes in the way science is taught to incorporate ethics into recognized scientific theory and practice, these concerns will not be adequately addressed.

Keywords: Donor animals, Ethical issues, Immunological barriers, Religious considerations, Xenotransplantation

Introduction

Despite the fact that there are over 135,000 transplants carried out annually throughout the world, this still only accounts for less than 10% of the true global needs for failing organs (such as kidneys, skin, testicles, hearts, livers, lungs, bones, small bowels, and pancreas, etc.) due to a lack of donors. This is true even though living donor transplants have been performed since the 1960s [1]. This fact has prompted medical professionals and researchers worldwide to develop a "bridge the gap" technique called xenotransplantation (cross-species transplantation, implantation or even infusion of live cells, tissues or even organs, especially from pigs and nonhuman primates to humans) in order to provide an immediate and limitless supply of transplantable organs that could aid in the treatment of many disorders [1; 2].

While an in-depth discussion of the history of numerous successful clinical attempts at xenotransplantation is impractical for the current review paper, it is important to highlight the key contributions that helped the field get to where it is nowa shining example of the power of science and medicine working together for the greater good. The cultural backdrop of xenotransplantation, religious beliefs, ethical considerations, desirable qualities of donor animals, challenges that the xenotransplantation procedure faces, and the influence of xenotransplantation on zoonotic risk are all briefly reviewed in this study.

Another important consideration is the potential for the spread of diseases from animals to humans. Because the cells, tissues, or organs used in xenotransplantation come from another species, there is a risk that they may carry diseases that are not present in humans. This could potentially lead to the spread of new diseases or the exacerbation of existing ones. To minimize this risk, it is important to carefully screen the cells, tissues, or organs before they are used in xenotransplantation, and to implement strict protocols to prevent the spread of disease. Despite these challenges, researchers are continuing to explore the potential of xenotransplantation as a way to overcome the shortage of human allografts.

In the future, it is likely that advances in science and technology will make it possible to overcome many of the challenges currently facing xenotransplantation , paving the way for its wide–spread use in clinical transplantation.

Chimeras in folklore

Historically, Folklore had long contained accounts of chimaeras (i.e. monstrous creatures composed of parts of multipleăspecies) before the technique of xenotransplantation was even considered. People were sporadically shown in prehistoric cave paintings, but the sole example of a human is a man with a bird's head in the Lascaux cave in France (about 15,000 BC), which is where the stories of vampires and werewolves (half man, half beast) originated. The Great Sphinx of Giza (about 2500 BC) features a lion body with a human head in contrast to the gods of Ancient Egypt (Anubis), who were commonly depicted with a human body and an animal (jackal) head. Additionally, a Sanskrit document from the 12th century BC has the first account of xenotransplantation in Indian mythology, which describes Ganesha, a huge infant with an elephant-like head (a son of two Indian gods, Shiva and Parvati). In addition, xenotransplantation was depicted in Greek mythology through the likes of the Minotaur (a man with a bull head), Esfinge (a winged lion with a woman head), and Centaurs (horses with a man's head and trunk), as well as in Homer's Odyssey, which featured chimaeras that were half-swine, half-man (about 750 BC) [3; 4; 5; 6].

History of clinical experiences with xenotransplantation

The idea of human xenotransplantation attempts actually got started in the 17th century with the first attempt to transfuse sheep blood into people in 1667 (Figure **??**)[7]. In reality, scientists and doctors are unable to create true human-animal chimaeras followed by an opacified human cornea was replaced with a transparent porcine cornea [8] and a kidney xenotransplantation from a rabbit occurred in 1905 [9; 10], the clear pig cornea was then used to replace an opaque human cornea, and in the early 1970s, successful corneal xenotransplantations from fish and gibbons were performed [10; 11]. Additionally, a clinical study of kidney xenotransplantation from a chimpanzee to humans was conducted between 1963 and 1964 [12]. This was followed by the first attempts at heart xenotransplantation from chimpanzee and baboon donors in 1964 [13] and 1984 [14], respectively. Using baboon donors, the first successful liver xenotransplantation procedure was carried out in 1992 [15]. Clinical xenotransplantation experiments have not been conducted in the United States or the majority of European nations since the 1990s because of certain xenozoonoses, immunological concerns, surgical effectiveness, and other regulatory concerns [16]. But according to reported reports, between 2013 and 2017 China and Russia used xenotransplantation to cure diabetes patients using transplanted neonatal pig islets [17].

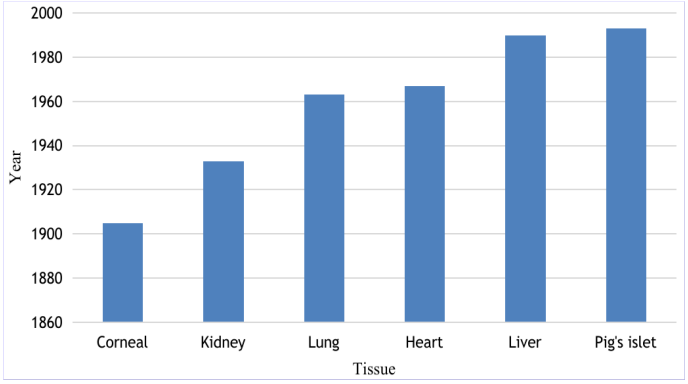

Figure 1. Historical recorded trials concerning xenotransplantation in different organs.

Blood xenotransfusion

If we delve beyond myth and folklore, we find Jean Baptiste Denis started the therapeutic practise of transfusing animal blood into humans [18; 19]. Results were conflicting and not surprising. Consequently, xenotransfusion was outlawed in France for a while. A strong case could be made for using pigs as a source of blood cells and blood products (if they are maintained in ideal "clean" conditions and are periodically checked to ensure no infectious agent is being passed) given the current threat of infectious pathogens being transferred and the need for future human blood transfusions [19]. In actuality, this method has been reevaluated by a number of studies [20].

Blood vessel anastomosis

More scientific developments had to wait until the 20th century, when French experimental surgeon Alexis Carrel devised surgical methods for anastomosing blood arteries, enabling the first successful organ transplant to occur. Carrel worked first in France and subsequently in North America [21].

Skin xenotransplantation

Various animal species and humans began using skin grafts in the 19th century when either pedicle or free skin grafts were used as the skin transplants. The donor, which may be a sheep, a rabbit, a dog, a cat, a rat, a chicken, or a pigeon, had to stay immobile while connected to the patient for a period of days so that the recipient could reportedly vascularize the graft. The perfect transplant would have looked like it was taken from a frog since they occasionally had "skinned alive" skin. When used to cover skin ulcers, it's likely that some of these grafts were "successful" in the sense that they provided protection, at least for a few days, as the ulcer healed below them. But it's likely that none of the grafts turned out to be long-lasting [22; 23].

Corneal xenotransplantation

Corneal xenotransplantation, the process of transplanting corneas from one species to another, has a long and fascinating history.

The first recorded corneal xenotransplantation was actually performed from a human to a dog in 1838 by Dr. Samuel D. Gross [24]. However, it wasn't until 1905 that the first corneal allograft, a transplant from a person to a pig, was successfully completed [10; 25].

Since then, the field of corneal xenotransplantation has made significant progress, with various animal species, including pigs, rabbits, and monkeys, being used as potential donors [26]. Despite these advances, the use of animal-derived corneal grafts in humans remains controversial, with concerns surrounding the potential transmission of diseases, the ethical implications of using animals as organ donors, and the potential immunological reactions of the recipient [27].

Despite these challenges, research into corneal xenotransplantation continues, with the hope of eventually finding a reliable and safe alternative to human corneal transplantation, which is currently limited by the shortage of donor tissue [28].

Cell xenotransplantation

Serge Voronoff, a Russian immigrant who settled in Paris, had the concept of transplanting cells that produced a hormone that the recipient lacked. Given the small number of human pancreases that become available each year, there is tremendous interest in utilising pig islets for this. But for older guys who had lost their "zest for life," Voronoff's main goal was to slow down ageing. He implanted chimpanzee or baboon testicles into a sizable number of male human patients [29; 30]. His method involved cutting the animal testicle into slices and inserting the pieces into the testicles of the recipients. On both sides of the Atlantic, the treatment gained popularity, and several hundred of these surgeries were carried out. It is improbable that any of them had any positive effects besides psychological ones, yet there have been tales of extraordinary "rejuvenation" in men who have undergone surgery and reported having considerably more energy. Because donor testicle slices may have necrosed and created infectious or inflammatory problems occasionally, the surgeries must have had significant complications. Furthermore, the first kidney allotransplant was carried on 1933 [31] John Brinkley maintained the concept of transplanting goat glandular tissue to produce hormones that the recipient would benefit from in the United States [32]. Nevertheless, the development of several clinics, particularly in Europe, where patients get injections of animal tissue or serum to treat a variety of disorders has ensured that the concept of cell xenotransplantation has endured to the current day. Controversy has been created by the results [33].

Xenotransplantation of the kidney

By the 1960s, Keith Reemtsma of Tulane University in Louisiana had proposed that transplanting human recipients with nonhuman monkey kidneys might successfully treat renal insufficiency. At that time, French and American surgeons had spent a lot of effort on the concept of kidney transplantation, but there were not enough deceased person kidneys accessible, and chronic dialysis had not yet been invented. So long as organs from nonhuman animals couldn't be procured, Reemtsma thought the patient had no alternative but to pass away. He decided to get the organs from chimpanzees because of their close evolutionary relationship to humans. He carried out 13 of these transplants, each of which included giving the patient both kidneys from a chimpanzee (which generally weighs considerably less than an adult human) [12]. During autopsy, the chimpanzee kidneys showed no abnormalities or signs of acute or enduring rejection. The notion of employing non-human primates as kidney donors was pioneered by several surgeons, most notably by Tom Starzl who used baboons as donors in Colorado [34], and his findings were comparable to those of Reemtsma. Others had insignificant contacts in the US and France [35].

Xenotransplantation of the heart

When James Hardy visited Reemtsma in 1963 and conducted the first human lung allotransplant, he was struck by the recipients of chimpanzee kidney transplants who were all in good condition. Hardy decided to buy some chimpanzees as possible "donors" in 1964 in order to execute the first clinical heart transplant in the event that he was unable to find a deceased human donor. He had a less-than-ideal patient who would not be allowed for heart transplantation today due to his patient's significant atheromatous vascular disease, for which he had both of his legs amputated, and the fact that he was semicomatose at the time the surgery was carried out. However, the patient's rapid decline prompted Hardy to perform a chimpanzee heart transplant [21]. Because the chimpanzee heart was too tiny to maintain the circulation, it failed within a short period of time. Contrary to the attempted lung allotransplantation, the heart xenotransplantation received a negative response from the public and medical community, which deterred Hardy and his colleagues from trying again. The heart allotransplantation procedure was later developed by Barnard and his collaborators in 1967 [21]. Later, they carried out two heart xenotransplantations [36].

Lung xenotransplantation

Only the Maryland team has lately engaged in active lung xenotransplantation research. Platelet sequestration and activation during GTKO was discovered by [37]. The hCD46 pig lung perfusion by human blood was mostly caused by GPIb, GPIIb/IIIa, and von Willebrand factor. GTKO is reduced by transgenic expression of the human leukocyte antigen (HLA-E). The hCD46 pigs with xenograft pulmonary injury. Ex vivo human blood perfusion models of the lungs of genetically altered pigs with drugs that suppress complement activation, coagulation, and inflammation dramatically improved lung xenograft survival in vivo [38].

Liver xenotransplantation

Tom Starzl, one of the most important pioneers in the area of kidney and liver allotransplantation, tried a few liver transplantations on young patients and nonhuman primates in Colorado in

the 1960s without long-term success [39; 40; 41]. In the 1990s, he and his Pittsburgh team performed two liver transplants from baboons in adult patients, with one patient enduring 70 days of survival after tacrolimus was added to the immunosuppressive arsenal [15]. The results, however, were not convincing enough to warrant continuing this exploratory clinical trial. The pig [42] and other nonprimate mammals have been used in a few efforts, but they haven't been very effective. Most early attempts at therapeutic organ xenotransplantation obtained their organs from nonhuman primate species [35].

The first islet xenotransplantation

An estimated 2 to 3 million persons in the United States alone have type 1 diabetes. Since pig insulin varies from human insulin by just one amino acid and has been used successfully to treat diabetic patients for decades before recombinant human insulin became available, it is reasonable to anticipate that normoglycemia will result from a successful pig islet transplant. The first effort at pig islet transplantation in diabetic patients was undertaken in 1993 by a Swedish team under the direction of Carl Groth [43].

Features of the perfect donor animal include

When we analyse the ideal qualities of animals suitable as organ donors for humans, a large list forms. The animal's anatomy and physiology must first be compatible with humans for the desired organ to work well in them. The risk of an infection from one species (i.e., an animal) to another should also be eliminated. Even human viral infections would not be able to pass through an excellent animal donor organ. This animal species should also be inexpensive to feed and produce because to its short gestation periods and frequent births each litter to achieve economies of scale. Additionally, no immunologic obstacles to transplanting into humans should be present in such an animal. Finally, there shouldn't be much ethical debate about using this animal in this way. There is no animal species that satisfies all of the aforementioned requirements. Apes and monkeys are nonhuman primates that resemble humans the most anatomically and physiologically. They might also be resistant to some human diseases. In reality, because of their hepatitis B and HIV resistance, baboon liver xenografts have been used in research [15]. But the xenotransplant community appears to have given up on the idea of utilising nonhuman primates as xenograft donors, mainly due to the hazards of infection for human patients and those who come in contact with them. Some monkey viruses, like herpes 8, can kill people in a couple of days [44]. It is thought that raising pathogen-free herds in sufficient numbers to satisfy therapeutic demand would be prohibitively costly. Last but not least, using nonhuman primates as human organ donors has serious ethical problems [45; 46]. Due to its large litter sizes (up to 10 littermates), short gestation periods (4 months), anatomical and physiological similarities to humans, widespread use for human consumption (an estimated 90 million pigs are consumed annually in the USA), and lengthy history of providing medicinals (skin, insulin, cardiac prostheses, and clotting factors) for humans, the pig has emerged as the most likely candidate for consideration as an organ donor. Undoubtedly, considerable hurdles may arise due to significant discrepancies in the coagulation cascade and other aspects of porcine physiology [47; 48]. Even though they are becoming more recognised, immunologic obstacles still need to be overcome.

Table 1. The benefits and drawbacks of using pigs vs baboons as a source of organs and cells for people, as described by [18].

Comparison	Pig	Baboon
Organ size in adults	Sufficient	Insufficient
Maintenance costs	Significantly inferior	Elevated
Human anatomy similarities	Moderately related	Very related
Human-like physiological similarities	Moderately related	Very related
Accessibility	Adequate	inadequate
Relation with the immune system to humans	Distant related	Very related
Data of tissue typing	Significant (in selected herds)	Inadequate
Age of sexual maturity	4-8 months	3-5 years
Breeding potential	Good quality	Poor quality
Pregnancy period	114 ± 2 days	173-193 days
Offsprings per time	5-12	1-2
Development	Fast (adult human size within 6 months)	Sluggish (9 years to reach maximum size)
Blood type compatibility with humans	Probably insignificant	Vital
Knowledge of genetic engineering	significant	None
Risk of transfer of infection (xenozoonosis)	Low	High
Availability of specific pathogen-free animals	Yes	Yes
Public opinion	More in favor	Mixed

In addition, several diabetes treatments, such as immunosuppressive regimes and pancreatic islet transplantation procedures, were initially developed using the dog model. Primate models with induced diabetes are being used more frequently as a result of recent developments toward the use of monoclonal antibody treatments for immunosuppression in human islet transplantation. Researchers in several domains are thinking about using naturally occurring illness models in client-owned pets in addition to induced-disease models in large animals. This article will discuss how naturally existing canine diabetes can be used as a translational model for creating islet transplants for diabetic patients who are humans [49].

Other pharmaceuticals of animal origin

In Table 2 we provide a list of various xenotransplantation products and their origins, generic names, product names, and therapeutic class. The table includes products from a variety of animal sources, including horses, pigs, mice, cows, and others.

One of the key observations from the table is the wide range of therapeutic applications for xenotransplantation products. These products are used to treat a wide range of conditions, including respiratory problems, anticoagulants, antivenoms, and vaccines. This highlights the potential benefits of xenotransplantation as a way to overcome shortages of human allografts and provide treatments for a variety of medical conditions.

Another interesting aspect of the table is the diversity of animal sources used in xenotransplantation. The table includes products from horses, pigs, mice, and cows, among others. This

suggests that a wide range of animals can be used as sources for xenotransplantation products, depending on the specific needs of the recipient and the availability of appropriate cells, tissues, or organs.

Overall, the table provides a useful overview of the past, present, and future directions of xenotransplantation. It highlights the potential benefits of using xenotransplantation products in clinical transplantation, as well as the ethical considerations and technical challenges that need to be addressed in order for it to be widely used.

In addition to the observations mentioned above, the table also highlights the potential challenges of xenotransplantation. For example, one of the main challenges is ensuring that the cells, tissues, or organs used in xenotransplantation are compatible with the recipient's immune system. If the transplant is rejected, it may be necessary to use immunosuppressive drugs to prevent rejection, which can have negative side effects for the recipient.

Another challenge is the potential for the spread of diseases from animals to humans. Because the cells, tissues, or organs used in xenotransplantation come from another species, there is a risk that they may carry diseases that are not present in humans. This could potentially lead to the spread of new diseases or the exacerbation of existing ones. To minimize this risk, it is important to carefully screen the cells, tissues, or organs before they are used in xenotransplantation, and to implement strict protocols to prevent the spread of disease.

Despite these challenges, the potential benefits of xenotransplantation are considerable. In the future, it is likely that advances in science and technology will make it possible to overcome many of the challenges currently facing xenotransplantation, paving the way for its widespread use in clinical transplantation. This could help to alleviate the shortage of human allografts and provide new treatment options for a variety of medical conditions.

Issues with several xenotransplantation cases

Complications include immunological incompatibility, cell death, abnormal cell differentiation and proliferation, virus transmission from animals to humans, and ethical concerns hinder the clinical application of xenogeneic stem cell transplantation [50].

Immune rejection

Immune rejection is unquestionably the problem with xenogeneic stem cell transplantation that worries people the most. Immunological rejection is avoided using the following methods: Only a few of the variables that need to be taken into account include the use of cellular desensitisation technology, immunosuppressive medications, suitable stem cell type selection, gene editing technology, encapsulated cell technology, the use of immunosuppressive drugs, and the regulation of cytokine levels. These procedures have increased the success rate of transplantations. Selecting stem cells with low immunogenicity, immunosuppressive, and immunomodulatory traits may help to alleviate this problem [51]. Injected immunocompetent mice with stem cells obtained from human umbilical cord stroma. The results showed that this kind of human stem cell has immunosuppressive and immunomodulatory properties [51]. Later research showed that xenogeneic stem cells, in particular xenogeneic MSCs, have low immunogenicity along with immunosuppressive and immune-modulatory capabilities [52]. Porcine MSCs have been used in xenotransplantation investigations because to their low immunogenicity attributes and immunomodulatory qualities [53]. Pig umbilical cord MSCs and swine ESC-derived neural progenitors were implanted in non-immunocompr–omised rats [54]. Their investigation revealed similar cell immunosuppressive effects [53]. The potential of these cells to suppress the immune system and have minimal immunogenicity was proven by the transplantation of rabbit umbilical cord MSCs with hyaluronic acid/tricalcium phosphate scaffolds in rats [55]. By co-implanting rat MSCs and pig neuroblasts in immunocompetent rat striata, [52] demonstrated the immunosuppressive characteristics of these cells. According to study by [56], rat ADSCs can protect themselves from human xenoantibodies and complement-mediated lysis. Gal, or galactose-1, 3-galactose, is related with low expression and this capacity is CD59 dependent [56].

Hyperacute rejection

Antibodies that are spontaneously generated against blood type antigens are similar to xenoreactive natural antibodies (XNA). The epitope that these antibodies primarily target is the non-reducing trisaccharide group galactosyl a-(1, 3)-galactosyl b-1,4-N-acetyl glucosaminyl, also known as the gal epitope15. Man does not have this epitope because he lacks the enzyme that makes it. Higher primates thus recognise the gal epitope as "non-self" and produce an immune response to it. Numerous microbes16 contain the gal epitope, and humans are exposed to the antigen through their guts, where they develop anti-gal antibodies. The key mechanisms by which XNA exerts its effects include natural killer (NK) cells, complement activation, and endothelium phenotypic alterations. The goal of research to date has been to lessen the effects of XNA [60; 61].

Acute humoral xenograft rejection (AHXR)

The following challenge is delayed xenograft rejection, which is frequently seen. The primary histological features of AHXR are endothelial swelling or disruption, vascular thrombosis with blood extravasation, and interstitial oedema [62]. Within 24 hours of transplantation, this generally develops, gets worse over the next few days, and finally kills the graft. The first response, which is mostly but not solely specific for the gal epitope, is mediated by IgM, and is thereafter followed by an increase in IgG levels [63]. By themselves, these xenograft natural antibodies induce a procoagulant state that develops into disseminated intravascular coagulation. Even the best practises for limiting complement activation, lowering T-cell and B-cell driven immune responses, and diminishing xenograft natural antibodies

Table 2. Different pharmaceutical products derived from non-human mammalian cells as represented by [57; 58; 59].

Origin	Generic name	Product name	Therapeutic class
Equine (Horse)	Conjugated oestrogen	Premarin	Gonadal hormone, Oestrogen
	Antithymocyte Immuglobulin (ATG)	ATGAM	Immunosuppressant
	Snake antivenom	Red back spider antivenom	Antivenom
		Tiger snake antivenom	
		Green Pit Viper Antivenin	
		Sea snake antivenin	
		Cobra Antivenin	
		Taipan antivenom	
		King Cobra Antivenin	
		Polyvalent Snake Antivenin	
	Medroxyprogesterone acetate	Premia	Gonadal hormone
	Stonefish antivenom	Stonefish antivenom	Antivenom
Porcine (Pig):	Coagulation factors II, IX, X, V & VII	Prothrombinex-VF	Haemostatic agent
	Heparin sodium	Heparinised saline	Anticoagulant
	Amylase, lipase, pancrelipase, protease	Panzytrat	Digestive supplement
	Poractant alfa	Curosurf	Respiratory agent
	Danaparoid	Orgaran	Haemostatic agent
	Human rotavirus live attenuated vaccine	Rotarix	Vaccine
	Dalteparin	Fragmin	Anticoagulant
	Rotavirus vaccine live oral pentavalent	RotaTeq	Vaccine
	Pancrelipase pancreatin	Creon	Digestive supplements & cholelitholytics
	Enoxaparin	Clexane	Anticoagulant, Antithrombotics
	Zoster virus vaccine live	Zostavax	Vaccine
	Vancomycin Hydrochloride	Vancomycin HCl	Antibiotic, miscellaneous
Murine (Mouse)	Trastuzumab	Herceptin	Antineoplastic agent
	Cetuximab	Erbitux	Antineoplastic agent
	Infliximab	Remicade	Monoclonal antibody
	Antihemophilic Factor VIII (human)	Hemofil M	Antihemophlic Agent
	Bevacizumab	Avastin	Antineoplastic agent
	Rituximab	MabThera	Antineoplastic agent; Monoclonal antibody
	Golimumab	Simponi	Antirheumatic agent
	Abciximab	Reopro	Anticoagulant
	Palivizumab	Synagis	Immunomodifier
	Somatropin	Saizen	Pituitary hormone
	Basiliximab	Simulect	Immunomodifier
Bovine (Cow)	Epinephrine	Adrenaline	Neurotransmitter
	Sealerprotein solution+ thrombin solution	Tisseel VHS/D Solution	Haemostatic agent
	Collagen	Zyderm Collagen implants	Dermatological preparations
	Calfactant	Infasurf	Treatment of premature infant lungs
	Hepatitis A vaccine	Vivaxim	Vaccine
	Allantoin	Allantoin	Cosmetics, treatment of wounds & ulcers
	Polygeline	Haemaccel	Plasma volume expander
	Varicellazoster vaccine, live	Varivax	Vaccine
	Calporo	Calporo	Herbal daily supplements
	Insulin	Hypurininjection	Insulin preparations
	Bovine colostrums	Travelan	Anti-diarrhoeal
	Survanta	Beractant	Treatment of premature infant lungs
	Cartilag	Cartilag	Herbal analgesics & anti-inflammatories

Continued on next page

Table 2. – continued from previous page.

Origin	Generic name	Product name	Therapeutic class
Bovine-manufacture	Acitretin	Novatretin	Antipsoriatic
	Measles, mumps & rubella vaccine	Priorix	Vaccine
	Itraconazole	Itrazol	Antifungal, azole derivative
		Inox	
	Mebeverine HCl	Mebetin	Antispasmodics
	Amoxycillin	Synamox	Antibiotic, Penicillin
	Loperamide	Colodium	Antidiareal
		Modim	
	Mycophenolate Mofetil	Cellcept	Immunosuppressant agent
	Essential Phospholipids	Livovid	Cholelitholytics
	Rabies vaccine	Merieux	Vaccine
		Rabipur	
	HepatitisAvaccine	Avaxim	Vaccine
		Havrix	
	Hydrocortisone	HydrocortisonOrion	Corticosteroid
	Clindamycin HCl	Tidact	Antibiotic, Lincosamide
	Recombinant antihaemophilic factor	Recombinate	Haemostaticagents
	Nilotinib	Tasigna	Antineoplastic agent, thyroxine kinase inhibitor
	Clofazimine	Fazim	Antibiotics, Leprostatic
	Ampicillin Sod+ Sulbactam Sod	Unasyn	Antibiotic, Penicillin
	Rabies human diploid cell vaccine	Verorab	Vaccine
	Hepatitis B vaccine	Engerix-B	Vaccine
	Omeprazole	Omeprazole	Gastric acid secretion inhibitor, proton pump inhibitor
	Calcitriol	Osteocap	Vitamin D Analog
	diphtheria, tetanus & acellular pertussis vaccine	Adacel	Vaccine
	Cyclosporin	Sandimmun	Immunosuppressant, Calcineurin inhibitor
	Pneumococcal vaccine	Prevenar	Vaccine
	Doxycycline	Xidox	Antibiotics, Tetracyclines derivatives
	Celecoxib	Celebrex	NSAID, Cyclooxygenase-2 inhibitor
	Phenytoin sodium	Dilantin	Anti-epilepsy
	Dutasteride	Avodart	5-alpha-reductase inhibitor
	Oseltamivir phosphate	Fluhalt	Antiviral, influenza, neuraminidase inhibitor
	Diphtheria toxoid	ADT Booster	Vaccine
		Boostrix	
	Pancreatin	Creon	Pancreatic enzyme replacement
	Danazol	Nazo	Androgen
	Oxycodone HCl	Oxynorm	Opioids analgesic
	Pregabalin	Lyrica	Anticonvulsant
	Didanosine	Aurobindo	Antiretrovirals
	Haemophilus B influenzae vaccine	Hiberix	Vaccine
	Heparin sodium injection	Heparinol	Anticoagulant
	Isotretinoin	Acnotin	Anti acne, antineoplastic agent
	Recombinant antihaemophilic factor	Recombinate	Haemostatic agents
	Influenza virus vaccine	Fluarix	Vaccine
	Tacrolimus	Prograf	Immunosuppressant agent
	Fluconazole	Fluconazole	Antifungals
	Rivastigmine	Rivadem	Acethylcholinesterase inhibitor
	Gem fibrozil	Gem fibrozil	Dyslipidaemic agents
	Yellow fever vaccine	17D vaccine	Vaccine

Continued on next page

Table 2. – continued from previous page.

Origin	Generic name	Product name	Therapeutic class
Egg/Chicken	Measles, mumps and rubella virus vaccine l	M-M-R II	Vaccine
	Influenza virus vaccine	Agrippal	Vaccine
	Measles, mumps and rubella virus vaccine	Priorix	Vaccine
	Measles, mumps, rubella and varicella vaccine	Priorix-Tetra & ProQuad	Vaccine
	Rabies vaccine	Rabipur	Vaccine
	Coxiella burnetii vaccine	Q-Vax & Q-Vax Skin Test	Vaccine
	Influenza virus vaccine	Vaxigrip	Vaccine
	Risperidone	Rixadone	Antipsychotic agent
	Verteporfin	Visudyne	ophthalmic medication
	quadrivalent influenza vaccine	Afluria Quad	Vaccine
	Propofol	Propofol Sandoz Propofol-Lipuro 1%/2% Provive 1% & Provive MCT-LCT 1%	Anaesthetics
	Yellow Fever Vaccine	Stamaril	Vaccine
	Olive oil and soya oil	Clin Oleic 20%	Parenteral vitamins, minerals and nutrition
	Sebelipase alfa	Kanuma	endocrine and metabolic agent
	Influenza virus vaccine	Fluarix	Vaccine
	quadrivalent influenza vaccine	Fluad Quad	Vaccine
	Quadrivalent Influenza Vaccine	FluQuadri	Vaccine
	Influenza virus vaccine	Fluad	Vaccine
	trivalent influenza vaccine	Fluzone HighDose	Vaccine
	Clevidipine	Cleviprex	Antihypertensive agent
	Influenza virus vaccine	Influvac	Vaccine
	Propofol	Diprivan	Anaesthetics
	Propofol	Fresofol 1% Injection & Fresofol 1% MCT/LCT	Anaesthetics
	Soya oil	Intralipid	Parenteral vitamins, minerals and nutrition
Chinese hamster ovary (CHO) cells	Aflibercept	Eylea	Ophthalmic medication
	Follitropinalfa	Gonal-f	Pituitary hormone
	Erythropoeitin alfa	Binocrit	Hematopoietic agent
	Laronidase	Aldurazyme	Enzyme replacement therapy
	Abatacept	Orencia	Immuno-modifier
	Interferon beta-1a	Avonex	Immunomodifier
		Rebif	
	Omalizumab	Xolair	Other respiratory agent
	Etanercept	Enbrel	Tumour necrosis factor inhibitor
	Panitumumab	Vectibix	Antineoplastic agents
	Eptacog alfa	NovoSevenRT	Haemostatic agent
	Octocogalfa	Advate	Haemostatic agent
		KogenateFS	
	Lenograstim	Granocyte	Supportive therapy
	Follitropinbeta	Puregon	Pituitary hormone
	Nonacogalfa	BeneFIX	Haemostatic agent
	Lutropin alfa	Luveris 75 IU	Pituitary hormone
	Imiglucerase	Cerezyme	Enzyme replacement therapy
	Dornasealfa	Pulmozyme	Respiratory agent

Continued on next page

Table 2. – continued from previous page.

Origin	Generic name	Product name	Therapeutic class
	Dornasealfa	Pulmozyme	Respiratory agent
	Alemtuzumab	Mabcampath	Antineoplastic agent
	Trastuzumab	Herceptin	Antineoplastic agent
	Choriogonadotropin alfa	Ovidrel	Pituitary hormone
	Tenecteplase	Metalyse	Fibrinolytic agent
	Darbepoietin	Aranesp	Haemopoietic agent
	Recombinate antihaemophilic factor	Recombinate	Haemostatic agent
	Agalsidasebeta	Fabrazyme	Enzyme replacement therapy
	Epoietin alfa	Eprex	Haemopoieticagent
	Rituximab	Mabthera	Antineoplasticagent
	Methoxy polyethylene glycol-epoetinbeta	Micera	Hematopoietic agent
	Denosumab	Prolia	Monoclonal antibody
		Xgeva	
	Moroctocogalfa	Xyntha	Haemostaticagent
	Epoetin lambda	Novicrit	Haemopoieticagent
	Bevacizumab	Avastin	Antineoplastic
	Epoietin beta	NeoRecormon	Haemopoieticagent
	Corifollitropin alfa	Elonva	Pituitary hormones
Sheep	Box Jellyfish Antivenom	Box Jellyfish Antivenom	antivenom
	Digoxin binding antibody Digoxin-specific antibody fragment	DigiFab	Antidote
Fish, Shark and Shell fish	house dust mite extract	Acarizax	Antiallergy preparation
	Chondroitin	Chondroitin	Complementary osteoarthritis
	Inactivated influenza vaccine	Fluad	Vaccine
	Glucosamine	Glucosamine	Complementary osteoarthritis
	Phleum pratense.	Grazax	Antiallergy preparation
	Insulin	Human Insulin (rys) & Protaphane Mixtard 30/70. Mixtard 50/50	Insulin preparation
Rabbit	Funnel web spider antivenom (rabbit)	Funnel Web Spider Antivenom	antivenom

sometimes fall short of addressing these issues. Diffuse intravascular coagulation and thrombotic microangiopathy, which are related to postpone xenotransplant rejection, are caused by unknown processes. AHXR is the least well-known of the early xenograft rejection phases [64].

Cell proliferation, aberrant differentiation, and death

Similar to the problems with cell replacement treatment, cell death and abnormal cell differentiation and proliferation directly led to the failure of xenogeneic stem cell transplantation and even injured the recipients. Researchers have shown that the microenvironment of the cell culture affects cell differentiation and death. Several researchers have attempted to change the microenvironment of the cells to prevent cell death and abnormal differentiation. Here, we will discuss two common methods for changing the microenvironments of cell cultures to resemble the in vivo natural growth niche. One tactic is to change the traditional two-dimensional (2D) culture into a three-dimensional (3D) culture. Umbilical cord MSC single-cell derived spheres were produced by [65] using cell chips, a device to restrict cells to specific spatial locations. They combined a 3D culture with a 2D arrayed pattern of single or multiple cells on one patch of the cell chip in order to improve MSC survival and migratory ability and to promote angiogenesis in xenotransplantation [65]. The other technique requires changing the scaffold. Materials used as scaffolds in tissue engineering xenogeneic stem cell transplantation may promote cell survival and differentiation. [66] employed a hyaluronic acid-based scaffold that has been covalently modified by poly-l-Lysine as a delivery vehicle to deliver hBMSCs to rats with injured spinal cords. Rats receiving hBMSCs/hyaluronic acid-poly-l-Lysine showed improved in vivo survival of transplanted hBMSCs, according to [66]. In contrast, when sheep MSCs were injected into immunocompromised rats, a ceramic hyaluronic acid/tricalcium phosphate carrier led to ectopic osteogenesis, adipogenesis, and hematopoietic-support activities [67]. The necessity of selecting an adequate substrate for tissue creation while taking into account the anticipated direction of cell differentiation was established by these findings [67]. iPSCs and ESCs may be tumorigenic due to their capacity for cellular growth in cell transplantation and other treatments. This problem was addressed by [68] by implementing optimised directed differentiation protocols to generate the desired precursor cell types and by using cellular enrichment techniques to eliminate unnecessary cells in order to choose only the cells with a restricted proliferation potential for transplantation.

Religious restrictions

In Table 3 we provide information about the restrictions on xenotransplantation products in different countries based on the religions practiced in those countries. It is important to note that these restrictions are based on the beliefs and practices of individual religions and do not necessarily reflect the views or laws of the countries in which they are practiced.

One of the main observations from the table is that many religions place restrictions on the use of certain animal products. For example, Islam prohibits the use of porcine products and requires that all animal products be slaughtered in a specific way. Similarly, Judaism prohibits the use of porcine and shellfish products and has strict rules about the types of land animals, birds, and fish that can be consumed. Hinduism and Sikhism also place restrictions on the use of animal products, with many Hindus abstaining from all animal products and Sikhs prohibiting the use of halal sources.

Another important aspect of the table is the diversity of religions represented. The table includes information about Islam, Judaism, Seventh Day Adventism, Hinduism, Sikhism, and Jehovah's Witnesses, among others. This highlights the fact that religious beliefs and practices can vary widely and may influence the use of xenotransplantation products in different parts of the world.

Overall, the table provides useful information about the potential restrictions on xenotransplantation products based on the religions practiced in different countries. It is important to consider these restrictions when developing and implementing xenotransplantation treatments in order to respect the beliefs and practices of different religious communities.

Ethical concerns

Ethics around xenogeneic stem cell transplantation are becoming more widely accepted. Some people believe that xenotransplantation consistently transgresses the lines between species and lowers the dignity of humans. Animal welfare organisations also opposed xenotransplantation on the grounds that nonhuman creatures shouldn't be seen of as re-designable systems [70]. In reality, a wide range of animal products are now used by humans. For instance, bioactive bones from decellularized bovine femoral bone and freeze-dried bone marrow stem cell paracrine factors are widely used in large-sized bone lesions. These successes are gradually changing people's opinions and paving the way for xenogeneic stem cell transplantation. However, any applications must consider regional variations in culture, legislation, beliefs, and other factors [71].

Risk of zoonotic infections

Potential benefits of xenotransplantation over allotransplantation (transplantation between members of the same species) include an almost limitless supply of grafts, animal species resistance to certain human infections (baboons, for example, are immune to the hepatitis B virus (HBV) and the human immunodeficiency virus (HIV)), and the ability to lower the risk of xenograft-associated infections by using specific pathogen-free animals with lifelong controversies, and the ability to reduce the risk of xenograft [72; 73]. However, if the risk to public health arises from introducing novel zoonotic infectious diseases into the human population that aren't typically present there, the prospect of spreading germs from animals to people via xenotransplantation cannot be completely precluded [74]. The characteristics of

Table 3. Religious restrictions as published by others [59; 69].

Religion	Countries where widely practiced	Restrictions
Islam	Indonesia, India, Pakistan, Bangladesh, Egypt, Turkey, Iran, Nigeria, Ethiopia, Afghanistan, Sudan, Iraq, Malaysia, Tanzania, Somalia, Cote dIvoire, Congo, Philippines, Sierra Leone, Thailand, Eritrea, Lebanon	Porcine products prohibited All animal products not killed in the prescribed ritualistic way (halal) prohibited Products containing alcohol prohibited
Judaism	USA, Israel, France, Canada, UK, Russia, Argentina, Ukraine, Brazil and South Africa	All porcine and shellfish products prohibited . other rules about animal products that can be ingested: land animals must be mammals which chew their cud and have cloven hooves birds of prey are prohibited . Fish must have scales and fins. Meat and milk (or any other dairy product) cannot be combined; shrimp and other non-fish seafood are forbidden. Observers follow a stringent set of regulations and only eat kosher food.
Seventh Day Adventist	Australia, USA, South America, some African countries	Some abstain from meat, but eggs are permissible.
Hinduism	India, Nepal, Bangladesh, Indonesia, Pakistan, Sri Lanka, Philippines, Fiji, UK, Mauritius, Bhutan, South Africa, Burma, Singapore	For the vast majority of vegetarians, all animal products, including eggs, are forbidden. Bovine and porcine goods continue to be prohibited for persons who are not vegetarians.
Sikh	India, Pakistan, Malaysia, Singapore, Fiji, New Zealand, USA and UK	For some who are vegetarian all animal products including egg prohibited For those who are not vegetarian, restrictions still include bovine and porcine products All animal products from halal sources prohibited Products containing alcohol prohibited.
Jehovahs witnesses	Australia, USA, Mexico, Brazil and many other countries (240 in total)	The use of fractions derived from the primary components of blood is not absolutely prohibited
Buddhism	Tibet, Bhutan, India, Nepal, Sri Lanka, Burma, Thailand, Laos, Cambodia, Malaysia, Vietnam, China, Bangladesh, Korea, Japan, Singapore, parts of Russia	For some vegetarian Buddhists - all animal products prohibited however, no fixed rules.

the particular organism, the amount of the organism transferred, the presence of the necessary equipment (such as receptors and nutrients in the host), and the immunological proficiency of the host all affect the likelihood of contracting a zoonotic infection. Even the wide range of potential clinical signs cannot be predicted for previously undetected animal-derived illnesses in human hosts [75].

Recipients and their contacts should be routinely screened for zoonotic infectious agents, either by direct methods (which depend on detecting the presence of the agent itself or its products) or even by indirect methods (which depend on detecting the production of antibodies against specific microbes and antigens) [76]. This is to prevent a potential new zoonosis from spreading among humans as a result of xenotransplantation.

Conclusion

Biotechnology has the power to drastically modify human existence, as we indicated at the beginning of our discussion and as the rise of xenotransplantation amply indicates. Furthermore, according to Gaskell's research, moral objections to biotechnology are allegedly more significant to society than even safety objections. Even non-problems, like "violating God's will" or "going against nature," are elevated to the status of the most severe ethical concerns as a result of society's lack of scientific and ethical understanding, which makes it challenging to come up with reasonable answers. Such an error might restrict the use of biotechnology to save lives and alleviate suffering, as our discussion has shown. This in turn emphasises the critical social illiteracy of science that we mentioned at the beginning of our argument, as well as the urgent need for expanded education of the general public, the scientific community, and society at large on ethics. Although it is relatively easy to see this issue, solving it is much more difficult. We have both taught and pushed for the inclusion of ethical considerations in science education as a necessary precursor to rational solutions to ethical difficulties arising out of scientific findings. We have also seen that such education produces better scientists who have a sense of social responsibility. Additionally, we have argued that it is critical to discuss and elucidate ethical issues while instructing students in science, particularly biological science. This has proven to be considerably more difficult. Obstacles to it include the fact that such an approach is historically uncommon and that the majority of scientists believe research is "value-free in general, and ethics-free in particular," as demonstrated in our debate. The majority of people who teach science do not have formal training in the ethical issues that arise from science or even how to start addressing such obstacles, which creates additional challenges. Determining when and how to begin integrating an ethical component into scientific instruction might be difficult as a result of these difficulties. The casual attitude of the research community toward the ethical issues associated to animal usage in research, which further distances the scientific community from the general people, is evident as social concern over the treatment of animals grows dramatically. If, as leaders in the scientific community have repeatedly remarked, scientific growth is entirely dependent upon the use of animals, then it is the responsibility of the scientific community to address social ethical concerns associated to animal exploitation. The development of animal ethics as we have described it is predicated on the notion of an animal, and society seems to concur with this. Furthermore, we brought this up throughout our discussion. The ethical viability of genetic modification, which is readily acknowledged to impact both large and small changes in telos, therefore inevitably arises. It is obvious that this is not the place for a comprehensive examination of this annoying problem. As long as the telos changes do not negatively affect the animals' quality of lifethat is, as long as the animals produced through genetic modification are not worse off than their unmodified forebears and, ideally, better offwe have argued that there is no morally wrong with carrying out such genetic modifications. In other words, it's important to make sure that animal genetic engineering doesn't do any harm. As with genetic alteration to fix genetic defects or prevent disease, the ideal outcome for animals is that they will be better off as a result of the change. Such problems will not be resolved unless major changes in scientists' thinking, which can only be made by significantly modifying the way science is taught, are made. At that point, ethics can be incorporated into recognised scientific theory and practise.

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