12-2022

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HNR 499-02: Honors Senior Project

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November 9, 2022

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For the thousands of patients in need of organ transplants, they know all too well that the supply of viable organs in the United States is critically low. Due to this shortage, medical institutions must decide who is most deserving of the organs that are available by filtering through patients' histories and conditions. In short, they must decide who is most worth saving. What if there was a way to solve this shortage? Thanks to advances in medical science, there may be a solution. Research has been conducted for a process that is being called xenotransplantation, which involves using cells and tissues from one organism and transplanting them to another. In theory, tissues or whole organs from other animals could be donated to humans in need of lifesaving organ transplants. However, there are many controversies surrounding this concept. Is it ethical to genetically modify animals and harvest their organs for our own benefit? Could doing so create another pandemic caused by a virus transmitted from humans to animals? Would living with another animal's organ inside a person alter their perspective of what makes them human? This project hopes to explore the complex ethical dilemmas behind xenotransplantation to spark a discussion about medical research and its impacts.

What is Xenotransplantation?

Through examining the makeup of the term, one could gather that the process of xenotransplantation involves the placement or transfer of some outside substance into another unrelated substance as the prefix of the word defines the foreign nature of the material being transplanted. More specifically, the United States Food and Drug Administration (FDA) defines the term as:

> Any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs (USFDA, 2021).

The *ex vivo* detail simply means that any human matter must come into contact with nonhuman animal matter outside of the human body before being transplanted into the human recipient. Initially, scientists believed that the ideal animal sources for this process were nonhuman primate (NHPs), which included animals like monkeys, baboons, and chimpanzees. This was a natural assumption due to evolutionary theory that shows humans and NHPs in close relation. However, researchers found that "despite their close phylogenic relationship with humans, NHPs were found to not be suitable for a number of reasons, including ethical concerns, costs, difficulties in generating genetic modifications, and biosafety" (Carrier et al., 2022). Surprisingly, the transition was then made for pigs to be used as the ideal animal specimen for xenotransplantation. Pigs are suitable for a multitude of reasons:

> Pigs are physiologically similar to humans, reach sexual maturity within several months and have large litter sizes, have a lower risk of zoonosis than NHPs and they can be reared under specific pathogen free (SPF) housing conditions further reducing risk of infections (Fischer and Schnieke, 2022).

Additionally, pigs are much less challenging to raise as compared to NHPs and techniques on rearing established through the farming industry can aid experimenters in cultivating mass populations of pigs in the most cost effective way possible.

Modification of Organs and the Challenges Posed

Before pig cells can be implanted into humans, the cells must be modified for compatibility with the human body. The target of this modification is the very code of life, the cell's DNA. Changing the DNA or genome is done by a Clustered Regularly Interspaced Short Palindromic Repeat, more commonly known as CRISPR, and a CRISPR associated (Cas-9) protein (Asmamaw and Zawdie, 2021). Together, these two form the CRISPR/Cas-9 genome-editing system. CRISPRs are small sections of the DNA where there is repetition within the code, and these sections of code can be cleaved by the Cas-9 protein to allow for inactivation or introduction of new genes (Asmamaw and Zawdie, 2021). Inactivation of existing genes or introduction of new ones modifies the pig organs to become more viable in a human host.

Once the cells have been modified, there are additional steps that must be taken before they are ready for human transplantation. To test how the human immune system will react to the genetically modified organ (GMO), the organ is placed in an "in vitro assay," which will run human blood serum through the organ (Fischer and Schnieke, 2022). Researchers carefully examine the in vitro assay to look for indicators of inflammation, cell apoptosis, or blood clot formation, all of which indicate that the human blood is mounting an immune attack against the modified pig organ. Once it is proven that the organ can thrive in the blood serum, the organ is then transplanted into a nonhuman primate for further testing. This validation step is called "in vivo" (Fischer and Schnieke, 2022). As previously discussed, NHPs are the closest animal relatives to humans, therefore, they make the ideal candidate for experimental transplantation before the modified pig organs can be approved for clinical use in humans. If all goes well, the organ will eventually be transplanted into a human recipient who will be closely monitored to assess the new organ's functioning and overall transplant success.

The Consequences of Improper Genome-Editing

Despite scientists' valiant efforts to prevent an immune flare-up or organ rejection, sometimes the modified pig organs are not compatible with the human body. When the human immune system mounts an attack against the transplanted organ, the organ can face one of three types of rejection: "hyperacute rejection, acute humoral rejection, and acute cellular rejection" (Carrier et al., 2022). Hyperacute rejection can occur "within minutes to few hours of transplant due to preformed antibodies in recipient's blood" (Carrier et al., 2022). These preformed antibodies in the human immune system will recognize a specific antigen on the surface of the pig cells that should have been repressed if genome-editing was successful. After recognition, the antibodies will group around the antigens, disrupting blood flow through the transplanted organ and impede proper functioning.

Should the organ survive the 24-hour mark, the risk of acute humoral rejection (AHR) is now a possibility. AHR is similar to hyperacute rejection in that it also involves a humoral response from human antibodies; however, AHR additionally recruits other immune cells to attack the foreign organ (Carrier et al., 2022). Lastly, the third type of organ rejection, acute cellular rejection, involves "NK [natural killer] cells, macrophages, neutrophils, T-cells and B-Cells" that attempt to destroy the transplanted organ (Carrier et al., 2022). Any one of these three types of rejection pose a major challenge for the success rate of genetically-modified organ transplants. It is crucial that scientists correctly edit the DNA of the pig cells to be supported by the human immune system, and it is equally important that the human recipient undergoes immune suppression in preparation to receive a foreign organ. According to Carrier et al. (2022), "a successful immunosuppression protocol should involve the combination of agents that can increase the length of transplant and have the least side effects on the recipient." The side effects

of rejection caused by a reaction with an improperly modified organ can have life-threatening effects on the patient.

Real-life, Human Cases of Xenotransplantation

Kidney Transplants from NHPs

In the 1960s, several smaller-scale experiments and procedures with xenotransplantation had been performed decades prior and proved mildly successful. Inspired by these cases, Keith Reemtsma of Tulane University hoped to prove that NHP kidneys could serve as suitable replacements for human kidneys. The NHP source he selected was the chimpanzee, harvesting kidneys from these animals and using them for thirteen transplant procedures (Cooper et al., 2015). As previously stated, NHPs were still believed to be the ideal non-human organ sources at the time as researchers had not yet discovered the potential of porcine organs. All but one of Reemtsma's transplants failed within four to eight weeks after the procedures, with the lucky patient surviving for nine months with a kidney from a non-human source (Cooper et al., 2015). Though the longest transplant case was ultimately deemed a failure due to the patient's eventual death, Reemtsma's experiments contributed greatly to the progression of xenotransplantation.

Baby Faye

One of the most well-known cases of cardiac xenotransplantation is the 1983 case of Baby Faye. Baby Faye was an infant girl that was born with a congenital heart defect that required immediate medical attention. Complicated procedures on infants are much more challenging to perform compared to fully-developed adults, however, the difficulty of the procedure was increased even more as "it was almost impossible to obtain human organs from infants" for use in transplants (Cooper et al., 2015). Desperate to save Baby Faye's life, Leonard Bailey instead replaced her diseased heart with the heart of a baboon. As noble as the surgeon's

intentions were, the procedure was for naught because “the graft underwent acute rejection and the patient died 20 days later” (Cooper et al., 2015). Understandably, the case of Baby Faye did not do much to promote the possibilities of xenotransplantation in the future of medicine. Instead, Cooper et al. (2015) argues that Bailey’s efforts brought the issue of organ scarcity to the public’s attention, especially for infants in need of transplants.

Recent Cases: 2021 and 2022

The field of xenotransplantation has made major strides in the past two years. Three recent cases have shown the life-saving potential of non-human organs and the outcomes of these cases emphasize the need for more research and funding for this growing field of medicine. Compared to the aforementioned procedures, two of the more recent cases differ in the fact that the patients receiving the modified organs were brain-dead. In September of 2021 at New York University, a modified porcine kidney was transplanted into the femoral blood vessels of a brain-dead patient at the permission of the patient’s family (Carrier et al., 2022). For many hours following the operation, the organ was “closely monitored and noted to make urine, clear creatinine, and show no overt signs of rejection” (Carrier et al., 2022). Using the results from this procedure, NYU performed another kidney transplant on November 22, 2021 in another brain-dead patient (DeVries, 2021). Similar to the September case, the kidney was assessed for functioning and rejection status and the results from the previous procedure were upheld in this second trial. Dr. Montgomery, the physician who led both of these operations, expressed, “There is much more work to do before we begin living human trials, but our preliminary findings give us hope” (DeVries, 2021). With more research, it is the hope of Dr. Montgomery and many other medical professionals, that xenotransplantation could remedy the national organ shortage.

The third most recent case marked a historic point in the timeline of xenotransplantation, as the transplantation of a porcine heart into a living human recipient was the first of its kind. The surgery took place on January 7, 2022, at the University of Maryland Medical Center (UMMC). The patient was David Bennet, a 57-year-old man who was in end-stage heart failure with no option for a traditional heart transplant. Bennet was rapidly declining in health before the surgery, "bedridden for eight weeks with a life-threatening arrhythmia and was connected to a heart-lung bypass machine;" he was able to be weaned from the machine and undergo rehabilitation after the transplant was performed (Kotz and Seiler, 2022). Bennet survived for two more months before finally succumbing to heart failure. As of June 2022, there were still ongoing investigations into the cause behind the failure of the porcine heart. Possible factors under consideration are an intravenous drug that contains antibodies that may have reacted poorly with the modified organ, and traces of a pig virus that could have caused an infection within Bennet's body (Kotz and Seiler, 2022). Many of the professionals involved in this transplantation were optimistic that Bennet's case brought xenotransplantation one step closer to clinical reality for patients in dire need of organ transplants.

Ethical Implications of Xenotransplantation

Xenotransplantation could be an exciting new solution to the organ shortage problem our nation currently faces. At the end of February 2022, the United States government estimated that there were around 116,690 patients that were awaiting organ transplant surgery, with the supply of readily available organs being nowhere near enough to satisfy this demand (Fischer & Schnieke, 2022). Once scientists perfect the process of xenotransplantation, biomedical facilities could produce enough genetically modified organs to close this gap. However, there are many

ethical concerns that are standing in the way of this breakthrough science advancing to medical reality.

The first major critique against xenotransplantation regards informed consent, a crucial element in any medical procedure. Informed consent involves a medical professional relaying information to a patient concerning the procedure they will undergo, the benefits and risks of said procedure, and if there are any alternatives to the treatment that has been proposed. The information must be phrased to not pressure the patient into a specific decision or present any biases a medical professional may hold. There are three standards that informed consent is typically judged by:

> (1) Subjective standard: *What would this patient need to know and understand to make an informed decision?* (2) Reasonable patient standard: *What would the average patient need to know to be an informed participant in the decision?* (3) Reasonable physician standard: *What would a typical physician say about this procedure?* (Shah et al., 2022)

There has been argument about the amount and adequacy of information that can be given to patients regarding xenotransplantation. Much is still unknown about animal organs being used in human bodies, therefore, some argue that patients cannot truly consent to a procedure as complex as this. Informed consent, according to Cozzi et al. (2021), can be complicated due to the "remaining uncertainties regarding the unintended effects of xenotransplantation" (p. 2014). Since physicians cannot fully understand how this kind of transplantation will affect a patient, how can we be sure that patients are receiving adequate information to make the decision to consent to this procedure? This issue continues to be pushed back and forth in major ethical committees as xenotransplantation cannot progress until informed

consent is improved, but informed consent cannot be improved until more research on xenotransplantation is done.

Introducing animal organs into human bodies raises the public health concern of outbreaks of zoonotic infections. The COVID-19 virus, theorized to have been passed from an animal to humans, is still a major public health concern after the pandemic saw its height in 2020. Though it has not yet been undeniably proven that COVID-19 is a zoonotic disease, the heightened public awareness of potential diseases that animals pass on to humans has been apparent. In relation to the issue of informed consent, there is not much information surrounding the probability of a human recipient contracting an infection from a modified animal organ. However, the risk does exist as research has discovered "porcine endogenous retroviruses can infect human cells in vitro" (Shapiro, 2022, p. 211). Regardless of the likelihood of a patient contracting a porcine retrovirus, the existence of this risk is enough to challenge the benefits that xenotransplantation proposes in fear of creating another global pandemic.

If the problem of zoonotic disease was eliminated and people with modified animal organs were able to survive and did not pose a health risk to others, how would their changed biology impact the definition of human? Though this question may seem exaggerative, this argument has surfaced in critiques of xenotransplantation. It is thought that implanting animal tissue and DNA into a human violates the biology and genome of the recipient, turning them into a sort of chimera. The National Cancer Institute (n.d.) defines a chimera as "tissue that contains cells with different genes than the rest of the person, organ, or tissue." Ultimately, what makes someone human is a subjective definition. With enough information, the patient will be able to decide for themselves if they can accept receiving an organ of non-human nature.

Many critiques of xenotransplantation focus on the effects on the patient, however, there are other concerns regarding the usage and treatment of animals for this science. Pigs that are being used for organ harvesting must be kept in laboratory settings and are subjected to experimentation and testing to become ideal candidates for organ transplant. To ensure ethical treatment of animals, there have been many legislative efforts passed protecting animal rights such as the Animal Welfare Act (AWA), passed in 1966. The main points of the act are as follows:

> Protects all warm-blooded animals except rats, mice, and birds bred for research. This includes zoos, circuses, research labs, hospitals, businesses, federal agencies, dealers, breeders, etc. Each research institution that uses a covered species must have an IACUC review all animal experiment protocols. The USDA licenses research facilities and conducts annual, unannounced inspections. Violations are punished with fines, cease-and-desist orders, and license suspension or revocation. (National Research Council, 2004, p. 33)

The IACUC, stands for Institutional Animal Care and Use Committee, is a committee created by the AWA to approve and oversee the use of animals in scientific research. This committee ensures that animals are being treated ethically during experimentation and that their use serves a purpose or obviously contributes to the advancement of medicine. However valiant their efforts are, some argue that these committees and regulations do not adequately protect animals. PETA, People for the Ethical Treatment of Animals, is an animal rights organization that vehemently argues against the use of animals for scientific research. They claim, “the majority of animal experiments do not contribute to improving human health, and the value of the role that animal experimentation plays in most medical advances is questionable” (PETA,

2022). It is difficult to argue against the frightening experience that animals face when used for experimentation, being raised in environments completely unnatural to them. However, xenotransplantation cannot be ruled out completely for the usage of animals when one considers the good that could come from this science. These animals, more specifically pigs, could be used to create organs for life-saving transplants and lessen the severity of the organ shortage crisis.

Conclusion

Xenotransplantation is far from becoming a commonplace treatment for organ failure, however, progressing research and recent documented cases of the procedure are promising. Though using non-human materials for medical purposes is not a novel concept, medical professionals have never been so close to seeing xenotransplantation become a reality as they were this year with a transplanted pig heart surviving two months in a human recipient. This breakthrough was met with many harsh criticisms including the inadequacy of informed consent in this kind of procedure, the risk-reward balance being disturbed with greater risks than benefits, and the exploitation of animals for scientific gain. The ethical and moral complexities surrounding the issue of xenotransplantation are likely to increase as research on the topic progresses, however, resolution of these ethical arguments may be possible with further discussion of the benefits and detriments of this experimental procedure.

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