Xenotransplantation ethics and history

Xenotransplantation is the procedure where live cells, tissues or organs from an animal are implanted, or infused into human patient. There are four different categories of xenotransplantation procedures which include; 1) Solid-organ xenotransplantation; where the source animal organ such as kidney or liver is completely transplanted into a human, 2) cellular and tissue xenotransplantation; where the transplantation of tissues and cells to the recipient happens without surgical connection of any animal blood vessels to the recipient's vessels, 3) extracorporeal perfusion; where human blood is circulated outside of the human body through an animal organ, such as a liver, or through a bioartificial organ produced by culturing animal cells on an artificial matrix, and 4) cellular and tissue xenotransplantation exposure to living animal-derived material; where human body fluids, cells, tissues or organs are removed from the body, come into contact with animals cells, tissues, or organs and are then placed back into a human. Xenografts have been proposed, as a way to transplant organs into recipients who are otherwise unable to receive human organs due to being excluded from the transplant list, or to cut down on the waiting time that someone has to wait to receive an organ.

The animal source which research on which xenotransplantation has focused mainly upon is the pig rather than other primates, although research on primates to be used for in xenografts has been carried out. This is mainly due to the ability to breed desired characteristics of the pigs (porcine), the fact that litters are reasonably large, gestation is fairly short which allows large numbers of animals in closed colonies, the fact that pigs are already being reared for food production and the ability to develop transgenic and

cloned animals, also the organs of pigs (porcine) are of similar size and physiology to human organs.

The first xenograft was said to have happened in the 1680’s when bone from a dog was said to have successfully been transplanted to repair the skull of a Russian aristocrat. It wasn’t till the 1960’s where xenotransplantation became a more systematic scientific study, where xenotransplantation and xenografts became a lot more than trial and error. In 1963 the first xenotransplantation took place in the US where baboon kidneys were transplanted into six patients, the six patients survived a maximum of 98days, also in 1964 chimpanzee kidneys were transplanted into twelve patients in the US. Most of these patients had the transplant fail within two months of the transplantation but one patient survived nine months. As well as the kidneys a chimpanzee heart was transplanted into a single patient, the patient only lasted for two hours after the procedure. Chimpanzee livers were also transplanted in children but these also didn’t survive long with the longest surviving for two weeks. The introduction to the immunosuppressant cyclosporine began in 1972; this is a strong immunosuppressant and is used in transplantation of organs so that the host body is less likely to reject the donor organ. In 1977 a 60 year old patient received a chimpanzee heart, but even with high doses of immunosuppressant drugs they managed to survive for only four days, but in 1984 a newborn baby received a baboon heart. Cyclosporine was used as an immunosuppressant but unfortunately only survived for twenty days. One of the most recent xenografts occurred in 1993 in which baboon bone marrow and kidneys were transplanted. A four-

drug cocktail was used to assist the transplant, but the suppressed immune system caused the patient to catch an infection and only survived 26 days.

Although xenotransplantation has had recent progress within the research done on porcine – human transplantation, it stills carries a potential risk of the transmission of infectious diseases that are both known and unknown to researchers, from the animal source to the human recipient. Some of the risks include; the transmission of pathogenic organisms into the human recipient that may not be detected within the source animal or may not be pathogenic to the source animal, the transmission of pathogenic organisms that would not normally be but are harmful to the human recipient when immunosuppressed or immunocompromised, and the risk of recombination of infectious agents to form pathogenic organisms. This is a type of xenozoonoses, where bacteria, parasites, viruses and fungi which could cause some rick to xenotransplants as they may be exchanged between the donor and the recipient via contact or in the case of PERVs within the donor's genome (Prabha, S. M., Verghese, S. 2008) At the moment Porcine Endogenous Retroviruses (PERVs) have been of some concern to researchers due to the ability to infect human cells in vitro and at the moment these cannot be removed from the source animal's genome, but to date studies of humans or non-human primates that exposed to live porcine tissue/cells have only been found to have a PERV infection or another other type of cross species infection detected although no disease has been reported (Esker, B. et al, 2008). It may be possible with systematic screening to find out if donor tissue contains supressed amounts of PERVs in vivo. This could cause transgenic donors to be bred with a lower risk of the donors carrying high

amounts of PERVs, which will allow for safer xenografts (Dieckhoff, B., Karlas, B. et al, 2006). It is also possible for the characterisation and mapping of PERVs in the many different breed of pigs, for example you may find that some strains of retrovirus is found in one species of pig but not in another or the location of the retroviruses may differ e. g. the locations of PERV-A and PERV-B on the chromosomes of Westran pigs and European Large White pigs (Lee, J. H et al, 2002). Like with allotransplantation (human donor to human host) there is always the risk that the host will reject the donor organ, there are four immunological barriers that must be overcome if xenotransplantation is going to be successful in the long run. These include hyperacute rejection, acute vascular rejection, T cell response and chronic xenograft rejection. Being able to understand the barriers that rejection causes e. g. in the case of hyperacute rejection in cardiac xenotransplantation can help overcome the rejection factors, though for other types of rejection this may not be the case (Dwyer, K. M., Cowan, P. J., d'Apice, A. J. F, 2002). Transgenic pigs may be seen as another way forward into overcoming the rejection barrier, the genetic modification of these pigs' means that they are able to be tailored to the specifications needed to allow xenotransplantation to occur for example tailoring them to lack the α-Gal antigen. This antigen is one of the main cause's hyperacute rejections. The ability to tailor and adapt these animals means that in the future further genetic changes will be used to help overcome other rejection mechanisms (Klymiuk, N, et al, 2010).

There have been many concerns and ethical issues that have been brought up about xenotransplantation. Many people are concerned about the health

of the recipient of the donor organ as well as the PERVs that are carried by pigs but also there are other human diseases that originated from animals before being transferred to humans e. g. Creutzfeldt-Jakob disease and AIDS. Although the main concern is the uncertainty that PERVs will not lead to unknown human diseases. Some ethical issues that have been considered include; the welfare to the donor animal from the breeding to the animal to the surgical procedure and aftermath (for example keeping them in conditions which they are not necessary accustomed to e. g. sterile conditions), whether we have the right to use animals for this reason, whether or not xenotransplantation causes humans to undesirably cross the human-animal boundary and that in some religions and cultures pigs are seen as unclean animals (e. g. Islam), as well as the fact that the animals may not be able to be seen as ‘ donors’ as there is no actual consent from the animals. The future of xenotransplantation and the likelihood of xenotransplantation becoming clinical studies depend on a range of things which include; the further modification of transgenic pigs, the introduction of immunosuppressant’s that only target the innate immune system and finally the development of methods that help induce donor specific tolerance in a clinical applicable way (Esker, B, et al, 2008).

Although there are risks when using organs or cells from an animal to a human, as well as the ethical side to the reasoning why we shouldn’t be using animal donors for transplants. Studies show that even with the stigma and ethics, that the majority of people would be happy to accept organs and cells from animal donors. The results gained from the study also looked at other factors such as age, education, the attitude to donating organs after

death, the descendents of the patient, the attitude in the use of animal stem cells for diabetes treatment and whether they have already received a failed organ transplant. The answers to these factors helped understand why people had a positive attitude towards xenotransplantation or not (Martínez-Alarcón, L., Ríos, A. et al, 2010).