

## Xenotransplantation for Renal Failure Patients: Evolution of Strategies

Editorial

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Although renal transplantation (RT) has improved quality of life and survival, organ shortage has led to expansion of waiting list and premature deaths. Over 100000 patients in the United States, similar number worldwide and over 7000 patients in the United Kingdom are waiting for RT. This has encouraged scientists to explore animals, xenotransplantation, as an alternative source of unlimited organ supply over the past three decades to overcome the chronic shortage of deceased and living human donors [1]. Successful xenotransplantation would eliminate the effects of brain death, ischaemia-reperfusion injury associated with prolonged preservation time and offer a potential for customise the donor organ before transplantation [2, 3]. However, successful clinical xenotransplant programme has not yet been established due to several physiological, immunological and microbial barriers besides ethical considerations.

Historically, in 1906, Mathieu Jaboulay was the first to transplant kidney of a pig, killed 3 hours previously, into the elbow (brachial artery and cephalic vein) of a woman suffering from nephrotic syndrome. The kidney produced 1500 mls of urine next day containing 16 g of urea. On the third day, the kidney was removed due to non-function, where histology confirmed vascular thrombosis and infarcted kidney and the patient died [4]. Keith Reemtsma and his colleagues from New York transplanted chimpanzee kidneys into 13 patients resulting in survival ranging from 11 days to 2 months, except for 1 patient who returned to work for 9 months before dying suddenly from electrolyte disturbances. At autopsy the transplanted kidney was normal both macroscopically and microscopically. The deaths in these patients were related to rejection and infection [5].

Non-human primates (NHP) such as chimpanzee and baboon are close relatives to human, but are not employed as organ donors, because former is an endangered species and the latter has smaller body size, infrequent O blood group, prolonged gestation period and small number of offspring and increased risk of transmission

of diseases [6]. Of all animals investigated, pig is considered as the best candidate for organ donation because of unlimited availability, favourable breeding characteristics and organs those have similar size and function to human counterparts. Current experiments in xenotransplantation models most often use pigs as the donor, and NHP as recipients [7].

The major problem of xenotransplantation was rejection post-transplantation due to the presence of preformed antibodies in the human and NHP and innate immune response (complement, coagulation and innate immune cells [e.g. monocytes, macrophages and NK cells]). To date 3 pig antigens have been identified in the vascular endothelium, the most important of which is galactose- $\alpha$ 1,3-galactose (Gal), the others being N-glycolylneuraminic acid (NeuGc) and the Sd(a) antigen [8]. The circulating antibodies present in the human and NHP against these antigens activate the complement system leading to generation of membrane attack complex, thereby causing hyperacute rejection and immediate loss of kidneys from genetically unmodified pig (wild type) within minutes [9]. In humans, the complement cascade is inhibited by membrane glycoproteins such as decay accelerating factor (DAF or CD55), membrane cofactor protein (MCP or CF46) and CD59, which are effective only with complement proteins of their own species [10].

A major progress in the genetic modifications has taken place to protect the pig tissues from the primate immune response by correcting the molecular incompatibilities between pig and primates. By employing nuclear transfer technique, the  $\alpha$ 1,3-galactose gene locus is knocked out, thus producing animals deficient in  $\alpha$ Gal epitopes and without target for anti- $\alpha$ Gal antibodies, thus the development of homozygous  $\alpha$ 1,3-galactosyltransferase knockout (GalT-KO) pigs have eliminated the barrier of hyperacute rejection [11, 12]. White and colleagues have successfully bred transgenic swine that express human DAF (h-DAF) and CD59 proteins on their vascular endothelium, thus inhibiting complement

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activation after transplantation of these organs [13].

With conventional calcineurin-based regimens, even with genetically engineered organ and high drug dosage, graft failure occurs within weeks from T-cell mediated rejection. T cell co-stimulation blockade (anti-CD154 mab or anti-CD40 mab) has increased the success rate [14]. Induction of T-cell tolerance to pig antigens by mixed chimerism and thymic transplantation is an important way forward [15, 16]. To suppress inflammatory response independent of adaptive immune response, administration of anti-interleukin 6 receptor agent tocilizumab, anti-tumour necrosis factor-alpha and production of genetically engineered pigs expressing an anti-inflammatory transgene (e.g., A20, Haem-oxygenase-1) have been examined [17, 18].

There has been progressive improvement in the survival of pig-to-primate RT model. In 1989, using genetically unmodified pig kidneys, the longest life-supporting kidney graft survival was 23 days. By 2004, kidneys from CD55 transgenic pig survive up to 90 days. In 2015, xenotransplant from a genetically engineered GalT-KO pig kidney to baboon has survived up to 136 days [19].

The porcine endogenous retroviruses are present in genome of every pig cells and will be transferred with the organ. However, the risk associated with the virus is small and techniques are now available whereby they could be inactivated or excluded from the pig [20]. The US Food and Drug Administration suggested that xenotransplantation should be restricted to patients with serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available. These might include those with a high degree of allo-sensitization to human leukocyte antigens or rapid recurrence of primary disease in previous allografts, such as focal sclerosing glomerulonephritis and membranoproliferative glomerulonephritis type II. It is not known whether recurrence of original disease occurs in the xenotransplant [21].

In summary, xenotransplantation has made major advances over past three decades and to date, no safety concerns that would definitely prohibit a clinical trial have been identified. The potential psychosocial, regulatory, and legal aspects of clinical xenotransplantation can be overcome when successful xenotransplantation has alleviated the stress related to allotransplantation, particularly deaths of patients while on the waiting list. Initially, clinical trial should include patients who are unable to obtain allografts, and subsequently extend the novel form of therapy to all patients in need of kidney transplant [22].

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