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# PROGRESS IN PIG-TO-NONHUMAN PRIMATE TRANSPLANTATION MODELS (1998–2013): A COMPREHENSIVE REVIEW OF THE LITERATURE

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## Abstract

The pig-to-nonhuman primate model is the standard choice for *in vivo* studies of organ and cell xenotransplantation. In 1998 Lambrigts and his colleagues surveyed the entire world literature and reported all experimental studies in this model. With the increasing number of genetically-engineered pigs that have become available during the past few years, this model is being utilized ever more frequently. We have now reviewed the literature again and have compiled the data we have been able to find for the period January 1st 1998 to December 31st 2013, a period of 16 years. The data are presented for transplants of the heart (heterotopic and orthotopic), kidney, liver, lung, islets, neuronal cells, hepatocytes, corneas, artery patches, and skin. Heart, kidney, and, particularly, islet xenograft survival have increased significantly since 1998, and the reasons for this are briefly discussed. A comment on the limitations of the model has been made, particularly with regard to these will affect progression of xenotransplantation towards the clinic.

### Keywords

Baboons; islets; monkeys; nonhuman primates; pigs; xenotransplantation; Cornea; Heart; Kidney; Liver; Lung; Nonhuman primate; Pancreatic islets

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**Statement re authors' contributions**

DKCC conceived the study. All authors contributed to the literature search and collection of data. DKCC and VS wrote the original draft, and all authors contributed to the final manuscript.

**Statement regarding conflict of interest**

The authors report no conflicts of interest.

## Introduction

Because of the immunologic similarities of Old World nonhuman primates (NHP), e.g., baboons, rhesus monkeys, and cynomolgus monkeys, to humans, the NHP represents the preferred surrogate for humans in exploring the response to pig organ or cell transplantation. The pig-to-NHP model was introduced into xenotransplantation research in the mid-1980s (1, 2), and has become the standard model for testing the primate immune response to organs and cells from pigs with genetic manipulations and/or the effect of novel immunosuppressive regimens.

Early experience in this model was comprehensively reviewed by Lambrigts et al., in 1998 (3), but has not been reviewed fully since then. With the aim of assessing progress in the 16 years that have elapsed since 1998, we have therefore attempted to search the literature for experience of pig organ (heart, kidney, liver, lung), islet, neuronal cell, hepatocyte, cornea, and artery patch transplantation. Others have relatively recently reviewed cornea (4–6) and islet (7) xenotransplantation, and their data have been included here. Brief mention has also been made of skin transplantation in the pig-to-NHP model. The early studies on the transfusion of pig red blood cells into nonhuman primates have been reviewed elsewhere (8), but have not been included here.

In 1998, the only genetically-engineered pigs available were those expressing a human complement-regulatory protein, e.g., CD55 (hDAF) (9). Research in the NHP model was greatly facilitated by the generosity of David White and his colleagues at Imutran and Novartis in making these pigs available to the research community.

The major innovations that have been introduced into the field since 1998 include (i) many new genetic modifications in pigs (reviewed by Ekser et al (10), including α1,3-galactosyltransferase gene-knockout (GTKO) pigs (11–15) and (ii) T cell costimulatory blockade agents, first introduced into NHP xenotransplantation models by Buhler et al., in 2000 (16). In 2013, the first pigs that did not express the important N-glycolylneuraminic acid epitopes (NeuGc-KO pigs) became available (17) but, as this oligosaccharide is expressed in all mammals except humans, its relevance cannot be explored in the pig-to-NHP model (discussed in (18)).

The literature has been reviewed from January 1st 1998 to December 31st 2013. On occasion, the same series of experiments has been reported in more than one paper, e.g., one reporting the overall results, one concentrating attention on the histopathology, etc. At times, it has been difficult to determine whether the experiments included in a report are the same as, or overlap with, those reported previously, and so there may be some duplication. If the report is of relevance to the pig-to-NHP model, we have attempted to be comprehensive, but we cannot guarantee we have included all publications.

We have not included reports of studies in NHPs that did not undergo organ or cell transplantation, e.g., immunoadsorption of anti-pig antibodies alone, or reports of *ex vivo* blood perfusion of pig organs, which has been a relatively common form of experimentation with regard to assessment of pig lungs and livers. Nor have we included bone marrow or hematopoietic cell xenotransplantation between pig and NHP unless it was associated with

an organ graft. We have not included papers published in languages other than English, nor abstracts of congresses, and have not always reviewed publications that did not present new data, or presented *in vitro* data from *in vivo* studies if the actual results of the transplants were not reported. If a short publication in *Transplantation Proceedings* was followed by a full publication in another journal, we have not always included reference to the preliminary publication.

## Heart xenotransplantation (Table 1)

More progress has been made in pig heart transplantation than in the transplantation of other vital organs. The introduction of GTKO pigs was important (reviewed in (19); hyperacute rejection, already minimized by the transplantation of hearts from pigs transgenic for a human complement-regulatory protein, was virtually eliminated, particularly when GTKO pigs expressed a human complement-regulatory protein. With adequate exogenous immunosuppressive therapy, the incidence of delayed xenograft rejection (acute humoral xenograft rejection, acute vascular rejection) was also greatly reduced. However, a new phenomenon, thrombotic microangiography, was reported (20), stimulating the development of pigs transgenic for one or more human coagulation-regulatory proteins, e.g., thrombomodulin, CD39, endothelial cell protein C receptor, which are only now being explored in the pig-to-NHP model.

In 1998, the longest survival of a heterotopically-placed (non-life-supporting) heart was reported to be 31 days (3), whereas by the end of 2013 this has been extended to >12 months (19,21–24) (Table 1A). Survival after othotopic (life-supporting) pig heart transplantation has been extended from a maximum of 19 days (3) to 57 days (Table 1B).

## Kidney xenotransplantation (Table 2)

Progress in the pig kidney-to-NHP model has been slower than in the pig heart-to-NHP model, though this conclusion may be misleading since the kidney is transplanted as a life-supporting organ whereas in the majority of cases the heart is transplanted as a heterotopic, non-life-supporting organ. However, the complications of consumptive coagulopathy appear to develop more rapidly when the kidney is transplanted (25). For reasons not fully understood, this model may therefore be a more difficult one than when the heart is transplanted. The longest life-supporting kidney graft survival in 1998 was reported to be 23 days (3), but this has been extended to 90 days (26).

With regard to co-transplantation of pig kidney and thymic tissue, which has resulted in a maximum kidney graft survival of 83 days (27), there have been studies of pig thymic grafts in NHPs in the absence of kidney transplants (28–31). Six baboons underwent a regimen aimed towards inducing tolerance, three of which received fetal or neonatal pig thymic tissue transplants (31). There was some *in vitro* evidence that the thymic tissue induced xenogeneic hyporesponsiveness.

## Liver xenotransplantation (Table 3)

Special problems relating to pig liver transplantation have proved a major barrier to progress, largely because the genetic manipulations of the organ-source pigs have to date largely been directed towards extending survival of heart and kidney grafts. The rapid development of thrombocytopenia in the recipient NHP following pig liver transplantation remains unresolved. Nevertheless, graft survival has been extended from <3 days in 1998 (3) to 10 days today (32).

## Lung xenotransplantation (Table 4)

The lung continues to provide major barriers, and considerable attention is currently being directed towards overcoming them. Most studies have been of ex vivo pig lung perfusion with human blood, which are not reviewed here. Despite major efforts, to date, pig lung graft survival after transplantation into NHPs has been extended only from 9 hours in 1998 (3) to 5 days today.

## Pancreatic islet xenotransplantation (Table 5)

More progress has been made in the transplantation of pig cells than pig organs. Although the instant blood-mediated inflammatory reaction remains a major barrier after islet transplantation into the portal vein, pig islet transplantation in NHPs has been successful for >1 year.

These reports and those for neuronal cell transplantation (see below) suggest that, with the possible exception of corneal xenotransplantation (see below), these cellular transplants are likely to be the first introduced into the clinic. Indeed, clinical trials of encapsulated wild-type pig islets have already been undertaken (33–35) but detailed reports have been scarce.

## Neuronal cell xenotransplantation

A field in which there were no reports in NHP models in 1998 is pig neuronal cell transplantation. Research has been largely limited to one European consortium, but graft function in monkeys with a Parkinson-like disorder has been documented for periods >1 year (36, 37).

## Hepatocyte xenotransplantation

Although the transplantation of pig hepatocytes may have some advantages over liver xenotransplantation, few studies have been undertaken in NHP models to date. However, hepatocyte function has been documented for >80 days after transplantation and for 253 days when a second transplant was performed (38).

## Corneal xenotransplantation (Table 6)

To our knowledge, no studies of pig corneal transplantation in NHPs had been reported before 1998, whereas a number of studies have been published since then, with encouraging

results. Anterior lamellar keratoplasty using decellularized corneas from wild-type pigs has resulted in graft transparency for >1 year.

## Artery patch xenotransplantation (Table 7)

Because of the development of thrombotic microangiopathy and/or consumptive coagulopathy, the assessment of immunosuppressive regimens or immunomodulatory approaches directed to the T cell response have been difficult to assess following pig-to-NHP organ transplantation. At our own center, Ezzelarab et al. have introduced a simple pig artery patch model which allows the adaptive immune response and, in particular, the production of T cell-dependent elicited anti-pig antibodies to be followed in the absence of the complicating factors of coagulation dysfunction (39). No such model had been reported in 1998, but today artery patch xenotransplantation is proving of value in assessing various immunosuppressive regimens.

## Skin xenotransplantation

In very complex experiments involving transduction of baboon bone marrow cells with SLA class II genes, followed by bone marrow transplantation and either pig kidney or skin transplantation, Ierino et al reported pig skin graft survival for 17 (control) or 21 days (40). Wiener et al reported prolonged GTKO pig skin graft survival in baboons (41). The GTKO skin grafts survived for up to 14 days whereas wild-type pig skin grafts were rejected by day 4.

## Discussion

In summary, we were unable to identify any reports on experimental studies of pig thymic tissue, neuronal cell, hepatocyte, corneal, skin, or artery patch transplantation in NHPs before 1998. Pig heart, kidney, and, particularly, islet graft survival have increased significantly since 1998. This has been associated largely with the increasing availability of pigs with genetic manipulations aimed at protecting the pig tissues from the primate immune response. Both GTKO and the introduction of human complement- and coagulation-regulatory transgenes have played a role, particularly with regard to heart transplantation. Although encouraging results have been achieved after the transplantation of wild-type pig islets into NHPs, the transplantation of islets from genetically-engineered pigs may allow a reduction in the intensity of the immunosuppressive therapy required to prevent graft loss.

Many successful immunosuppressive regimens in the pig-to-NHP model have been based on costimulation blockade with an anti-CD154 monoclonal antibody (mAb), which is unlikely to be available for clinical use because of its thrombogenic effects. Attention is now being directed towards replacing this agent with others, e.g., an anti-CD40 mAb (+/− an agent that blocks the CD28/B7 costimulation pathway). This problem will have to be resolved if approval for clinical trials is to be obtained by most national regulatory administrations, e.g., the Food and Drug Administration (FDA) in the USA. Recent studies by Mohiuddin and his colleagues (21–24) suggest that an anti-CD40 mAb-based regimen is likely to be successful, but this agent is not yet approved for clinical use. Blockade of the CD28/B7 pathway alone would appear to be inadequate (Iwase H et al, submitted).

A second topic that needs to be addressed before clinical trials are likely to be fully successful is that of expression of NeuGc in pigs (and in all NHPs), but not in humans (18). However, we would suggest that a successful GTKO pig transplant in a NHP provides an indicator of the likelihood of success of a GTKO/NeuGc-KO pig transplant in a human. We therefore continue to believe that the pig-to-NHP model provides very important data that cannot be obtained from *in vitro*, *ex vivo* perfusion, or other *in vivo* models. This particularly applies to the efficacy and safety testing of immunosuppressive protocols.

There are, of course, other differences in the biological (e.g., physiologic, immunologic) responses of NHPs and humans to transplanted pig organs, tissues, or cells, and resolutions to some of these may not be possible until clinical trials are undertaken. Nevertheless, we believe it is important to accumulate as many data from the pig-to-NHP model before proceeding to clinical trials, as this will provide the greatest likelihood of success. Whatever barriers identified in the pig-to-NHP model should be addressed before proceeding to the possibly more complex pig-to-human studies. Even though the management of a patient with a pig graft will undoubtedly be easier in many respects, failure from graft rejection or from the complications of excessive immunosuppressive therapy in the pig-to-NHP model is unlikely to be fully reversed in the pig-to-human model.

It is of interest to note the relative publication rates of the papers surveyed. For example, more papers relating to kidney xenotransplantation were published during the period covered by this survey than those relating to other organs. However, there was a marked reduction in the number of papers published after 2005 (Figure 1B). This may be associated with the increased problems related to pig kidney than to heart transplantation, where consumptive coagulopathy appears to be less problematic. However, after a peak period of publications in 2005, the rate of publication of papers reporting studies of pig heart transplantation also fell (Figure 1A).

The decline is possibly more likely a consequence of lack of sufficient funding for xenotransplantation research during the past few years, and this may also be a major factor in the reduction in publications relating to kidney transplantation after 2005 (Figure 1B). In turn, this decline in funding was at least in part associated with reluctance on the part of certain commercial/industrial sponsors to continue to participate in the development of xenotransplantation in view of the scares being propagated at that time relating to the transfer of porcine endogenous retroviruses (PERV) with the graft to the recipient. Since the first report of the potential of pig-to-human infection by PERV in 1996, much subsequent research has demonstrated that the risk of cross-species transmission is unlikely and, in any event, manageable (42). Of note, regulatory authorities are largely concentrating their attention on proper patient monitoring and archiving of samples rather than on preventing the introduction of xenotransplantation.

In contrast, pig islet xenotransplantation, which has provided very encouraging results, was reported fairly consistently throughout the period with between 1 and 4 publications per year (Figure 1C).

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## Abbreviations

| | |
|---|---|
| **Gal** | galactose-α1,3-galactose |
| **GTKO** | α1,3-galactosyltransferase gene-knockout |
| **mAb** | monoclonal antibody |
| **NeuGc** | N-glycolylneuraminic acid |
| **NHP** | nonhuman primate |
| **PERV** | porcine endogenous retroviruses |

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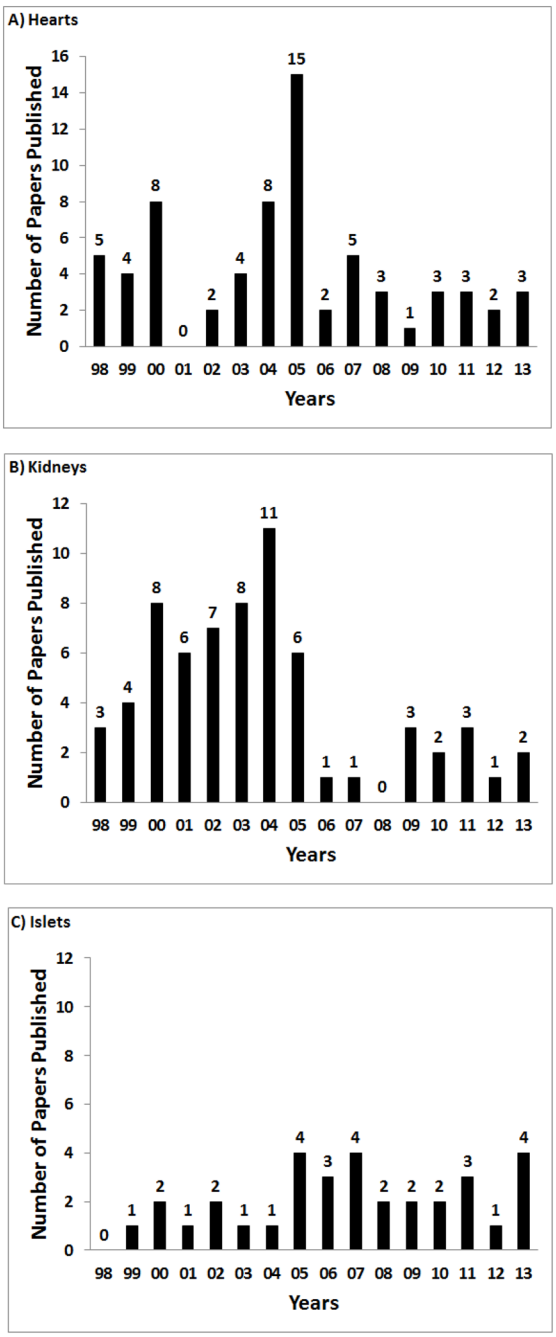


**Figure 1.**

Numbers of publications relating to pig-to-nonhuman primate heart **(A, top),** kidney **(B, middle),** and islet **(C, bottom)** transplantation during the period 1998–2013.

## Table 1A

Heterotopic transplantation of pig hearts in NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days, unless otherwise stated) |
|---|---|---|---|---|
| Simon (1998) | WT | Baboon (n=2) | Intravenous infusion of synthetic Gal oligosaccharides | <1 (4–6 hours) |
| Waterworth (1998) | CD55 | Baboon (n=3) | CyP, CsA, CS | >2, 13, >21 |
| Lin (1998) | CD55/CD59 | Baboon (n=5)<br>Baboon (n=6) | CyP, CsA, CS<br>CyP, CsA, CS, Ig-depleted (immunoadsorption column) | <1–5<br>1–29 |
| Bhatti (1999) | CD55 | Baboon (n=14) | CyP, CsA, CS, MMF | 10–99 (26) |
| Crespo (1999) | CD55 | Baboon (n=13) | Not stated | <3 (n=2)<br>3–7 (n=11) |
| Kozlowski (1999) | WT (MSw) | Baboon (n=2) | TBI, TI, pig BMTx, splenectomy, immunoadsorption, ATG, CsA, MMF, CS, 15-deoxyspergualin | 8, 15 |
| Romano (1999) | WT | Baboon (n=1) | Intravenous infusion of synthetic Gal ologosaccharide | <1 (<18 hours) |
| Buhler (2000)<br>Alwayn (2000) | WT (MSw) | Baboon (n=2) | TBI, TI, splenectomy, immunoadsorption, ATG, CVF, CsA or anti-CD154mAb, MMF or 15-deoxyspergualin (not clearly stated) +/− pig hematopoietic stem cells (n=1) | Not applicable (study of hemostasis) |
| Manez (2000) | WT<br>CD55 | Baboon (n=10)<br>Baboon (n=10) | None (n=5)<br>Immunoadsorption (n=5)<br>None (n=5)<br>Immunoadsorption (n=5) | <96 hours<br>87.6+/−35 hours<br>89.6+/−42 hours<br>101.6+/−23 hours |
| Lin (2000) | CD55/CD59 | Baboon (n=5)<br>Baboon (n=4) | CyP, CsA, CS<br>Immunoadsorption, CyP, CsA CS | <1–10 (3)<br>9–39 |
| Brenner (2000) | WT | Cynomolgus (n=1)<br>Rhesus (n=2)<br>Rhesus (n=4) | Immunoadsorption<br>Immunoadsorption<br>No immunoadsorption | }<br>}<br>}<br>}<br>140+/−35 minutes<br>78+/−28 minutes |
| Lam (2002) | CD55 | Cynomolgus (n=7) | CyP, CsA, CS, MMF | 6–36 (23) |
| Schuurman (2002) (based on previous publications) | WT (n=7)<br>CD55 (n=55)<br>WT (n=5)<br>CD55 (n=28) | Cynomolgus (n=62)<br>Baboon (n=33) | CyP, CsA, CS, splenectomy +/− rapa +/− MMF +/−sCR1<br>CyP, CsA, CS, splenectomy +/− rapa +/− MMF +/−sCR1 | WT: HAR 57%<br>CD55: HAR 7%<br>WT: HAR 20%<br>CD55: HAR 11%. |
| Ashton-Chess (2003) | CD55 | Baboon (n=2)<br>Baboon (n=2)<br>Baboon (n=9) | None<br>Immunoadsorption<br>Cyp, CsA, MMF, CS | 4, 5<br>4, 6<br>6–29 (14) |
| Domenech (2003a,b) | CD55 | Baboons (n=8) | CyP (high dose), CsA, CS, GAS914 (n=6)<br>CyP (low dose), CsA, CS, GAS914 (n=2) | 6–60 (27)<br>5, 7 |
| Lam (2003) | CD55 | Rhesus (n=2) | ATG, sCR1, tacrolimus, MMF, CS, GAS914 | <1 |
| Schirmer (2004) | CD46 | Baboon (n=9)<br>Baboon (n=9) | Anti-CD20mAb, tacrolimus, rapa, CS, TPC, clopidogrel, aspirin | 15–30 (22)<br>4–53 (15) |

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days, unless otherwise stated) |
|---|---|---|---|---|
| | | | Anti-CD20mAb, tacrolimus, rapa, CS, TPC | |
| Manez (2004a) | CD 55<br>CD55/CD46 | Baboon (n=5)<br>Baboon (n=5) | CsA, GAS914<br>CsA | 5–8 (6)<br>4–9 (7) |
| Manez (2004b) | WT<br>CD55<br>WT<br>CD55 | Baboon (n=5)<br>Baboon (n=6)<br>Baboon (n=5)<br>Baboon (n=7) | None<br>None<br>Immunoadsorption<br>Immunoadsorption | HAR in 3 of 5 3, 4<br>No HAR <1–<5<br>No HAR <2–5<br>No HAR <4–<6 |
| McGregor (2004) | CD46 | Baboon (n=10) | ATG, splenectomy, anti-CD20mAb, tacrolimus, rapa, CS, TPC | 56–113 (76) |
| Houser (2004)<br>Kuwaki (2004) | CD55 | Baboon (n=10) | ATG, anti-CD2mAb, TI, CVF, anti-CD154mAb, MMF, CS | 4–139 (27) |
| Lam (2004a)<br>Lam (2004b) | CD55 | Cynomolgus (n=15) | ATG or CyP, CsA or tacrolimus, MMF, CS, immunoadsorption, +/− GAS914 | No GAS914:<br>HAR in 4 of 6 4, 78<br>GAS914:<br>HAR in 0 of 9 0–36 (20) |
| Chan (2005) | CD55 | Cynomolgus (n=4) | CyP, CsA, MMF, CS, GAS914 +/− sCR1 | 20, 22, 35, 36 |
| Stalder (2005) | CD55 | Cynomolgus (n=6) | CyP or ATG, CsA or tacrolimus, MMF, CS, GAS914 +/− sCR1 | 2–36 (mean 30.5) |
| Teotia (2005) | CD46 | Baboon (n=16) | Anti-CD20mAb, tacrolimus, rapa, CS, TPC | 6–113 (mean 71) |
| Dor (2005)* | GTKO (MSw) | Baboon (n=8) | ATG, anti-CD154mAb, MMF, CS<br>ATG, anti-CD154mAb, MMF, CS, recombinant human antithrombin III | 16–179 |
| Kuwaki (2005)<br>Tseng (2005)<br>Hisashi (2008)<br>Shimizu (2008) | GTKO (MSw) | Baboon (n=8) | ATG, Anti-CD2mAb, TI, CVF, anti-CD154mAb, MMF, CS | >16–179 (63) |
| Moscoco (2005) | CD55<br>CD55/CD46 | Baboon (n=9)<br>Baboon (n=5) | CyP, CsA, MMF, CS, GAS914 (n=5)<br>CsA, GAS914 (n=4)<br>CsA, GAS914 | 50+/−19<br>6+/−1<br>6+/−2 |
| Weaver (2005) | CD46 | Baboons (n=8) | Anti-CD20mAb, tacrolimus, rapa, CS, TPC | 0–92 (64) |
| Wu (2005) | CD55<br>CD46 | Baboon (n=13)<br>Baboon (n=5) | CyP, CsA, MMF, CS +/− anti-CD20mAb +/− ATG +/− GAS914 or TPC (n=10)<br>ATG, anti-CD154mAb +/− anti-CD20mAb +/− CTLA4-Fc +/− GAS914 0r TPC (n=8) | 2–36 (12)<br>0–11 (6) |
| McGregor (2005) | CD46 | Baboon (n=7) | Splenectomy, ATG, anti-CD20mAb, tacrolimus, rapa, CS, TPC | 15–137 (96) |
| Byrne (2005) | CD46 | Baboon (n=9)<br>Baboon (n=13)<br>Baboon (n=9) | Splenectomy, anti-CD20mAb, tacrolimus, rapa, TPC, warfarin + ATG or CyP for rejection episodes<br>Splenectomy, anti-CD20mAb, tacrolimus, rapa, TPC, low molecular weight heparin+ ATG or CyP for rejection episodes<br>Splenectomy, anti-CD20mAb, tacrolimus, rapa, TPC | 3–62 (20)<br>5–109 (18)<br>4–53 (15) |
| Brenner (2005) | CD55 | Baboon (n=4) | Immunoadsorption, CyP, CsA, CS, MMF | 2–8 (10) |
| Davila (2006) | CD46 | Baboon (n=1)<br>Baboon (n=2)<br>Baboon (n=1) | Splenectomy<br>TPC, splenectomy<br>TPC, anti-CD20mAb, splenectomy | 5<br>6, 7<br>7 |

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days, unless otherwise stated) |
|---|---|---|---|---|
| Byrne (2006) | CD46 | Baboon (n=63) | Splenectomy, TPC, anti-CD20mAb, tacrolimus, rapa, CS +/− aspirin/ clopidogrel or Lovenox or warfarin | 0–139 (96) |
| Ricci (2007) (based on previous publications) | CD46 | Baboon (n=64) | Groups 1–4 (n=40): (Low maimtenance IS) Splenectomy, anti-CD20mAb, tacrolimus, rapa, CS, TPC +/− Lovenox or aspirin + clopidogrel or coumadin<br>Group 5 (n=15): (High maintenance IS) Splenectomy, anti-CD20mAb, tacrolimus, rapa, CS, TPC, Lovenox +/− ATG as induction of treatment of rejection | Groups 1–4: 0–137 (30)<br>Group 5: 0–139 (96) |
| Wu (2007) | CD55<br>CD46 | Baboon (n=20)<br>Baboon (n=3) | CyP, CsA, MMF (n=18);<br>ATG, anti-CD154mAb (n=10); GAS914 (n=8) or TPC (n=3)+/− immunoadsorption; complement inhibitors (n= 12) | Technical failure (n=1)<br>HAR (n=10)<br>Early graft failure 1–3 (n=4)<br>AHXR 6–36 (15) (n=8) |
| Zahorsky-Reeves (2007) | CD55 | Cynomolgus (n=3) | ATG or CyP, CsA, MMF, CS +/− GAS914 | 36, 39, 78 |
| Byrne (2008) | CD46<br>GTKO | Baboon (n=4)<br>Baboon (n=8) | Splenectomy +/− TPC +/− anti-CD20mAb<br>Splenectomy, ATG, anti-CD20mAb, tacrolimus rapa | 5–7<br>0–128 (25) |
| Ezzelarab (2009) | GTKO | Baboon (n=9) | ATG, CVF, anti-CD154mAb, MMF, CS | 2–56 |
| Bauer (2010) (Intrathoracic) | WT<br>GTKO/CD46 | Baboon (n=2)<br>Baboon (n=2) | None<br>ATG, anti-CD20mAb, tacrolimus, rapa, MMF, CS, bortezomib, immunoadsorption (n=1) | Euthanized after weaning from cardiopulmonary bypass<br><1, 50 |
| Tazelaar (2011) (partially based on previous publications) | CD46<br>CD46<br>GTKO +/− CD55 | Baboon (n=11)<br>Baboon (n=8)<br>Baboon (n=5) | ATG, anti-CD20mAb, tacrolimus, rapa, TPC<br>Immunoadsorption, CyP, CsA<br>ATG, anti-CD20mAb, tacrolimus, rapa | 15–109 (41)<br>8–42 (13)<br>18–71 (26) |
| Mohiuddin (2012)<br>Corcoran (2010)<br>Horvath (2010) | GTKO/CD46 | Baboon (n=2)<br>Baboon (n=2)<br>Baboon (n=9) | No IS<br>ATG, CVF, anti-CD154mAb, MMF, CS<br>ATG, anti-CD20mAb, CVF, anti-CD154mAb, MMF, CS | < 1<br>8, 8<br>36–236 (71) |
| McGregor (2012) | GTKO<br>GTKO/CD55 | Baboon (n=6)<br>Baboon (n=5) | ATG, anti-CD20mAb, tacrolimus, rapa, CS<br>ATG, anti-CD20mAb, tacrolimus, rapa, CS | <1–128 (21)<br>15–52 (28) |
| Kim (2013) | GTKO | Cynomolgus (n=4) | ATG, anti-CD20mAb, CVF, anti-CD154mAb, tacrolimus, CS | 11–24 (14) |
| Mohiuddin (2013) | GTKO/CD46 | Baboon (n=9) | ATG, anti-CD20mAb, CVF, anti-CD40mAb (either 3A8 [n=3] or 2C10R4 [n=6]), MMF, CS | 3A8 = 21, 21, 28 (21)<br>2C10R4 = >30, >40, 60, 107, 146, 149 (84) |
| Mohiuddin (2013/4) | GTKO/CD46/TBM | Baboon (n=5) | ATG, anti-CD20mAb, CVF, anti-CD40mAb, MMF, CS | 0–>380 (4 ongoing at 77–380 days) |

Abbreviations:

ATG = anti-thymocyte globulin; BMTx = bone marrow transplant; CD46 = membrane cofactor protein; CD55 = decay-accelerating factor; CD59 = protectin, membrane inhibitor of reactive lysis; CS = corticosteroids; CsA = cyclosporine; CTLA4-Fc = CTLA4 covalently linked to a human immunoglobulin Fc molecule; CVF = cobra venom factor; CyP = cyclophosphamide; EGF = early graft failure; GAS914 = a soluble

glycoconjugate comprising Gal on a poly-L-lysine backbone; GTKO = α1,3-galactosyltransferase gene-knockout; HAR = hyperacute rejection; IS = immunosuppressive therapy; LoCD2b = rat anti-primate CD2b monoclonal antibody; MMF = mycophenolate mofetil (or analog, e.g., mycophenolate sodium); MSw = miniature swine (MGH herd); Rapa = rapamycin (or derivative, e.g., RAD); sCR1 = soluble complement receptor type 1 (in some papers described as TP10); TBI = total body irradiation; TI = thymic irradiation, TPC= an αGal-polyethylene glycol polymer conjugate.

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## Table 1B

Orthotopic transplantation of pig hearts in NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days unless otherwise stated) |
|---|---|---|---|---|
| Schmoeckel (1998) | CD55 | Baboon (n=10) | CyP, CsA, CS | <1 (x5)<br>4–9 (x5) |
| Waterworth (1998) | CD55 | Baboon (n=5) | CyP, CsA, CS | >1, >1, 5, 5, 9 |
| Xu (1998) | WT | Baboon (n=2) | Immunoadsorption (through another donor organ), TBI, CsA, methotrexate, | 18, 19 |
| Brenner (2000a) | WT | Cynomolgus (n=2) | Immunoadorption | 130+/−21 minutes |
| Brenner (2000b,c) | WT | Baboon (n=4) | None (n=1)<br>Immunoadsorption (n=3) | 29 minutes<br><2, 11, 21 hours |
| Vial (2000) | CD55 | Baboon (n=1) | CyP, CsA, MMF, CS | 39 |
| Schuurman (2002) (based on previous publications) | CD55 | Baboon (n=16) | CyP, CsA, CS, splenectomy +/− rapa +/−MMF +/−sCR1 | HAR 1 (6%) |
| Brandl (2005) | CD55 | Baboon (n=4) | ATG, tacrolimus, rapa, CS, GAS914 +/−CyP | 1–25 (9) |
| Brenner (2005) | CD55 | Baboon (n=4) | CyP, CsA, MMF, CS | <1, 11, 13, 20 |
| Bauer (2005) | CD55 | Baboon (n=9) | ATG, tacrolimus or CsA, rapa, CS, GAS914, | Not stated |
| Brandl (2007) | CD46 or CD55 | Baboon (n=2)<br>Baboon (n=2)<br>Baboon (n=4)<br>Baboon (n=5) | ATG, tacrolimus, rapa, CS, GAS914<br>ATG, anti-CD20mAb, tacrolimus, rapa, CS, GAS914<br>ATG, low-dose CyP, tacrolimus, rapa, CS, GAS914<br>ATG, CyP, tacrolimus, rapa, CS, anti-HLA-DR antibody, +/− GAS914+TPC | 1, 9<br><2 (1 technical failure)<br><1, 14, 25 (1 technical failure)<br><1–4 |
| Bauer (2007) | CD55<br>CD46 | Baboon (n=6)<br>Baboon (n=6) | Not stated | Not stated |
| Bauer (2011) | CD46 | Baboon (n=6) | ATG +/− CyP, tacrolimus, rapa, CS, GAS914 or TPC, anti-HLA antibody | Not stated |
| Byrne (2011) | CD46 or CD55 or CTKO/CD55 | | ATG or CyP, tacrolimus, rapa +/− anti-CD20mAb +/− GAS914 or TPC | 0–57 (6) |

Abbreviations as for Table 1A

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**Table 2**

Transplantation of pig kidneys into NHPs (1998–2013)

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Ierino (1998) | WT (MSw) | Baboon (n=3) | TBI, BMTx (autologous, transfected with SLA class II [n=2]), splenectomy, apheresis, immunoadsorption, sCR-1, CsA, MMF, CS, 15-deoxyspergualin | 8, 12, 13 |
| Xu (1998) | WT (MSw) | Cynomolgus (n=10) | Immunoadsorption (Gal column n=4; pig liver n=6) | 2–12 (mean 7) |
| Zaidi (1998) | WT | Cynomolgus (n=6) | CyP, CsA, CS | <1–30 (7) |
| | CD55 | Cynomolgus (n=7) | | 6–35 (13) |
| Schmoeckel (1999) | CD55 | Cynomolgus (n=11) | Splenectomy, CyP, CsA, MMF, CS (n= 5)<br>CyP, CsA, MMF, CS (n=6) | Median 43<br>Median 15 (but 4 deaths with functioning kidney) |
| Ierino (1999) [Ierino (1998)] | WT (MSw) | Baboons (n=4; life-supporting in only one) | SLA class II gene transduction of baboon $CD34^+$ and $CD34^-$ bone marrow cells (n=3) | Uncertain |
| Kozlowski (1999) | WT (MSw) | Baboon (n=2) | TBI, TI, pig BMTx, splenectomy, Immunoadsorption, ATG, CsA, CS, MMF and/or 15-DSG | 9, 11 |
| | | Baboon (n=2) | As above (modified) | 3, 6 |
| Meyer (1999) | WT | Baboon (n=5) | Plasmapheresis, immunoadsorption | 1–5 (3) |
| | vWD | Baboon (n=5) | | 1–5 (4) |
| Loss (2000) | WT | Cynomolgus (n=7) | (Non-life supporting - study of effect of cold ischemia on HAR) | <1 |
| | | Cynomolgus (n=8) | Life-supporting - study of effect of cold ischemia on HAR) | <1 |
| Cowan (2000) | WT | Baboon (n=4) | None | <1 |
| | CD55/H-transferase | Baboon (n=2) | | 2 |
| | CD55/CD59/H-transferase | Baboon (n=2) | | 2, 3 |
| | | Baboon (n=4) | Low molecular weight heparin | 3–5 |
| Cozzi (2000) [Bhatti (1998)] | WT | Cynomolgus (n=5) | CyP, CsA, CS, splenectomy | 0–30 (0) |
| | CD55 | Cynomolgus (n=9) | CyP, CsA, CS, splenectomy | 5–78 (39) |
| | | Cynomolgus (n=7) | CyP, CsA, CS | 6–35 (13) |
| Dehoux (2000) | WT | Baboon (n=4) | None (splenectomy in 1) | <1 |
| | | Baboon (n=5) | anti-IgMmAb | 4–6 (4) |
| Buhler (2000) | WT (MSw) | Baboon (n=1) | TBI, TI, ATG, splenectomy, immunoadsorption, CVF, CsA or anti-CD154mAb, MMF or 15-deoxyspergualin (not clearly stated) | Not applicable (study of hemostasis) |

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| | | Baboon (n=3) | As above + pig hematopoietic cells | |
| Shimizu (2000) | WT (MSw) | Cynomolgus (n=4) | Immunoadsorption, splenectomy, CsA, 15-deoxyspergualin | 0, 1, 7, 8 |
| | | Cynomolgus (n=10) | As above + TBI, TI, ATG, BMTx (n=1) | 0–15 (9.5) |
| | | Baboon (n=2) | | 9, 11 |
| | | Baboon (n=4) | As above + TBI, TI, ATG, MMF or brequinar, BMTx (n=1) | 3, 6, 6, 14 |
| | | Baboon (n=5) | As above + TI, ATG (n=1), MMF, sCR1 or CVF, BMTx | 6–13 (8) |
| Kobayashi (2000) | WT | Baboon (n=2) | CyP, CsA or tacrolimus, CS, plasmapheresis | 6, 7 |
| | | Baboon (n=2) | As above + additional plasmapheresis | <1 |
| Loss (2000) | WT | Cynomolgus (n=8) | CyP, CsA, CS | 1–11 (3.5) |
| | CD55 | Cynomolgus (n=9) | | 1–68 (11) |
| Przemeck (2001) | WT | Cynomolgus (n=7) | CyP, CsA, CS | Not stated (study of cardio-circulary parameters) |
| | CD55 | Cynomolgus (n=6) | | |
| Bühler (2001) | WT (MSw) | Baboon (n=3) | Splenectomy, TBI, TI, ATG, immunoadsorption, CVF, anti-CD154mAb, MMF, CS | 4, 6, 8 |
| | | Baboon (n=2) | As above + CyP, but no TBI | 7, 13 |
| | CD55 | Baboon (n=3) | | 28, 29, 29 |
| Vangerow (2001) | CD55 | Cynomolgus (n=2) | CyP, CsA, CS | 3, 4 |
| | | Cynomolgus (n=4) | As above + treatment of rejection with CyP, CS | 9, 11, 11, 15 |
| | | Cynomolgus (n=4) | As above + treatment of rejection with CyP, CS, C1-INH | 18, 21, 28, 68 |
| Loss (2001) | WT | Cynomolgus (n=12) (donor kidney <50g) | CsA, CyP, CS: | <1–<15 (3) |
| | | Cynomolgus (n=3) : (donor kidney >70g) | CsA, CyP, CS | 1, 4, 11 |
| Loss (2001) | WT | Cynomolgus (n=7) | CyP, CsA, CS (Non life-supporting graft. Study on transmission of porcine endogenous retrovirus and porcine chimerism) | 4–287 (28) |
| | | Cynomolgus (n=5) | CyP, CsA, CS (Study on transmission of porcine endogenous retrovirus and porcine chimerism) | 1–11 (3) |
| Dean (2001) | CD55 | Baboon (n=5) | CyP, CsA, CS | 3–7 (mean 5+/−1) |
| | | Baboon (n=6) | Splenectomy, immunoadorption, CyP, CsA, CS | 6–12 (mean 10+/−1) |
| | | Baboon (n=3) | Splenectomy, intensive immunoadorption, CyP, CsA, CS | 13–15 (mean 14+/−0.3) |

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| McInnes (2002) | WT | Cynomolgus (n=11) | CyP, CsA, CS, splenectomy +/− rapa +/−MMF +/−sCR1 (Study on post-transplant lymphoproliferative disease) | <1–78 (6.5) |
| | CD55 | Cynomolgus (n=234) | | |
| Hecker (2002) | WT | Cynomolgus (n=3) | CyP, CsA, MMF, CS, C1-INH | 5, 13, 15 |
| Richards (2002) | CD55 | Cynomolgus (n=20) | CyP, CsA, CS +/−rapa +/−MMF +/−sCR1 | 4–60 (31) |
| Schuurman (2002) | WT | Cynomolgus (n=11) | CyP, CsA, CS, splenectomy +/− rapa +/−MMF +/−sCR1 | HAR: n=3 |
| | CD55 | Cynomolgus (n=234) | | HAR: n=0 |
| Ghanekar (2002) | CD55 | Baboon (n=2) | CsA, GAS914, CS, CyP, rapa | 20, 36 |
| | | Baboon (n=4) | ATG, CsA, GAS914, CS, rapa | 20, 22, 23, 26 |
| | | Baboon (n=3) | ATG, CsA, GAS914, CS | 18, 21, 22 |
| Dehoux (2002) | WT | Baboon (n=5) | Anti-IgM mAb | 4–6 (4) |
| Cowan (2002) | CD55/CD59 | Baboon (n=1) | Low molecular weight heparin | <1–6 |
| | | Baboon (n=3) | Low molecular weight heparin, recombinant human antithrombin III | |
| | | Baboon (n=1) | Recombinant human antithrombin III | |
| Zhong (2003) | CD55 | Baboon (n=4) | CyP, CsA, CS, rapa | 4, 4, 26, 40 |
| | | Baboon (n=12) | CyP, CsA, CS, rapa, GAS914 | 7–37 (14) |
| Barth (2003) | CD55 | Baboon (n=5) | (Thymokidneys), thymectomy/TI, splenectomy, immunoadsorption, anti-CD2mAb, ATG/anti-CD3IT, anti-CD154mAb, CyP, CVF, MMF, CS | 24–229 (27) |
| Gollackner (2003) | WT (MSw) | Baboons (n=2) | TI, splenectomy, immunoadsorption, ATG, anti-CD154mAb, CyP, CVF, MMF, CS | 7, 13 |
| | CD55 | Baboons (n=3) | | 28, 29, 29 |
| | WT (MSw) | Baboons (n=4) | As above + BSA-Gal | 8, 9, 11, 11 |
| Cozzi (2003) | CD55 | Cynomolgus (n=10) | Splenectomy, CsA, CyP, Cs, MMF | 2–51 (22) |
| Ashton-Chess (2003) | WT | Baboon (n=7) | Immunoadsorption, CyP, CsA, MMF, CS | 4–8 (5) |
| | CD55 | Baboon (n=4) | As above | 5, 5, 5, 9 |
| | CD55 | Baboon (n=4) | As above, but no immunoadsorption | 7, 8, 10, 12 |
| | CD55 | Baboon (n=4) | As above, but immunoadsorption x1 | 5, 5, 7, 10 |
| Cozzi (2003) | CD55 | Cynomolgus (n=5) | Methotrexate (6 doses), CsA, MMF, CS | 6, 9, 9, 10, 39 |
| | | Cynomolgus (n=3) | Methotrexate (4 doses), CsA, MPS, CS | 0, 16, 34 |
| | | Cynomolgus (n=2) | Methotrexate (5 doses), CsA, CS | 16, 41 |

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Gollackner (2003) | WT (MSw) | Baboon (n=3) | Immunoadsorption, splenectomy, TI, ATG, CVF, anti-CD154mAb, MMF, CS, CyP | 6, 7, 13 |
| | | Baboon (n=2) | As above + BSA-Gal | 8, 11 |
| | | Baboon (n=2) | As above + BSA-Gal, but no CyP | 9, 12 |
| Knosalla (2003) | WT (MSw) | Baboon (n=3) | Immunoadsorption, splenectomy, TI, ATG, CVF, CyP, anti-CD154mAb, MMF, CS | 6, 7, 13 |
| | CD55 | Baboon (n=3) | | 28, 29, 29 |
| Ashton-Chess (2004) | CD55/CD59 | Baboon (n=2) | None | 5, 6 |
| | | Baboon (n=4) | CsA, MMF, CS, mitoxantrone | 6, 7, 8, 10 (8) |
| | | Baboon (n=2) | As above, but CyP not mitoxantrone | 9, 9 |
| Loveland (2004) | WT | Baboon (n=7) | (Non-life-supporting) None | Not stated |
| | CD46 | Baboon (n=9 | | |
| Key (2004) | CD55 | Cynomolgus (n=52) | Various | 1–53 (17.5) |
| Lam (2004) | CD55 | Cynomolgus (n=4) | CyP, CsA, MMF, CS | <0, <0, <0, 4 |
| | | Cynomolgus (n=4) | As above + GAS914 | 6, 12, 31, 37 |
| Cozzi (2004) | CD55 (Donor pig pretreated with carbon monoxide) | Cynomolgus (n=5) | CyP, CsA, MMF, CS, GAS914 | 2–37 (12) |
| Baldan (2004) | CD55 | Cynomolgus (n=7) | CyP, CsA, MMF, CS | 1–90 (48) |
| | | Cynomolgus (n=10) | As above + methotrexate | 0–39 (13) |
| | | Cynomolgus (n=5) | As above + GAS914 | 7–38 (21) |
| | | Cynomolgus (n=6) | (Donor pig pretreated with carbon monoxide) As above + GAS914 | 2–37 (8.5)) |
| | | Cynomolgus (n=2) | As above + recombinant human antithrombin III | 23, 23 |
| Diaz (2004) | CD55 | Baboon (n=9) | Not stated | Not stated |
| Garcia (2004) | CD55 | Baboons (n=27) | CyP/ATG, CsA/tacrolimus, rapa/MMF, CS, GAS914 | 4–75 (mean 21) |
| Menoret (2004) | WT | Baboon (n=2) | None | <1 |
| | CD55/CD59 | Baboon (n=2) | | 5, 6 |
| Gollackner (2004) | WT (MSw) | Baboon (n=6) | WBI/CyP, IAD, SpX, TI, ATG, CVF, anti-CD154, MMF, CS | 4–13 (6.5) |
| | CD55 | Baboon (n=3) | | 28, 29, 29 |
| | WT (MSw) | Baboon (n=4) | Same, in addition BSA-Gal +/− CyP | 8, 9, 11, 11 |
| Ghanekar (2004) | CD55 | Baboon | Various (based on Ghanekar 2002 and Zhong 2003) | |

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Yamada (2005) | GTKO (MSw) | Baboon (n=6) | (Vascularized thymic lobe) +/−WBI, thymectomy, splenectomy, anti-CD2mAb, anti-CD154mAb, MMF, CS, +/− CVF | 4–68 (32) |
| | | Baboon (n=5) | (Thymokidney) As above | 16–83 (26) |
| | | Baboon (n=3) | (Kidney) As above | 20–34 (33) |
| Chen (2005) | GTKO | Baboon (n=3) | ATG, tacrolimus, CS | 8, 10, 11 |
| | | Baboon (n=3) | As above + MMF, CVF | 9, 13, 16 |
| Moscoso (2005) | CD55 | Baboon (n=8) | GAS914, CyP, CsA, MMF, CS | 11±9 |
| | | Baboon (n=5) | Anti-CD25mAb, FTY, CsA, CS | 12±10 |
| Sun (2005) | CD55 (from supplier A) | Baboon (n=4) | CyP, CsA, rapa | 4, 4, 26, 40 |
| | | Baboon (n=10) | As above + GAS914 | 9–37 (17) |
| | | Baboon (n=3) | ATG, CsA, rapa, GAS914 | 20, 23, 26 |
| | | Baboon (n=1) | ATG, tacrolimus, MMF, GAS914/TPC | 75 |
| | CD55 (from supplier B) | Baboon (n=5) | | 7–16 (13) |
| Shimizu (2005) | CD55 | Baboon (n=6) | (Thymokidney) Splenectomy, thymectomy/TI, immunoadsorption, ATG/anti-CD3IT, CyP, CVF, MMF, anti-CD154mAb | 9–27 (12) |
| | | Baboon (n=10) | | 2–30 (16) |
| Lam (2005) | CD55 | Cynomolgus (n=3) | CyP, CsA, MMF, CS, GAS | 6, 12, 31 |
| | | Cynomolgus (n=2) | As above + sCR-1 | 3, 15 |
| | | Cynomolgus (n=3) | As above + GAS914 + sCR-1 | 10, 20, 32, 37 |
| Chen (2006) | CD55 | Baboon (n=5) | GAS914/TPC, ATG, tacrolimus, MMF, CS | 7–75 (13) |
| | | Baboon (n=2) | GAS914/TPC, ATG, tacrolimus, CVF, anti-CD20mAb | 8,14 |
| Cavicchioli (2007) | CD55 | Cynomolgus (n=7) | CyP, CsA, MMF, CS | 1–90 (20) |
| | | Cynomolgus (n=8) | As above, but methotrexate not CyP | 0–39 (10) |
| Yazaki (2009) | CD55/endo-β-galactosidase C | Baboon (n=4) | Splenectomy, CyP, tacrolimus, CS | 2, 8, 9, 11 |
| Knosalla (2009) | WT (MSw) or CD55 | Baboon (n=6) | Not stated | Not stated |
| | GTKO (MSw) | Baboon (n=14) | (+/− vascularized thymic lobe or thymokidney) Not stated | |
| Griesemer (2009) | GTKO (MSw) | Baboon (n=7) | Thymectomy, splenectomy, TBI (n=1), ATG +/− anti-CD2mAb, anti-CD154mAb, tacrolimus, MMF, anti-CD20mAb | 18–83 (49) |
| Lin (2010) | WT | Baboon (n=1) | None | <1 |
| | GTKO/CD46 | Baboon (n=1) | | 2 |

| FIRST AUTHOR (YEAR) | DONOR (PIG) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL-RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| | WT | Baboon (n=1) | ATG, anti-CD154, MMF, CVF, CS | 6 |
| | GTKO | Baboon (n=1) | | 7 |
| | GTKO/CD46 | Baboon (n=1) | As above, but no CVF | 4 |
| | | Baboon (n=4) | As above, but no CVF or CS | 9, 10, 10, 16 |
| Griesemer (2010) | GTKO (MSw) | Baboon (n=2) | TBI, TI, splenectomy, ATG, anti-CD2mAb, tacrolimus, GTKO BMTx +/− CVF (n=1) | 8, 11 |
| Simioni (2011) | CD55 | Cynomolgus (n=2) | Extracorporeal kidney perfusion, GAS914, CyP, CsA, MMF, CS | 28, 55 |
| | | Cynomolgus (n=2) | As above + recombinant human antithrombin III + recombinant human activated protein C | 12, 34 |
| | | Cynomolgus (n=9) | As above + recombinant human activated protein C | 8–37 (20) |
| Nishimura (2011) | GTKO (MSw) | Baboon (n=2) | (Thymokidney) Thymectomy, splenectomy, anti-CD3IT +/−anti-CD2mAb, ATG, anti-CD20mAb, tacrolimus, MMF, anti-CD154mAb | 15, 15 |
| | | Baboon (n=2) | (Thymokidney) As above, but no anti-CD3IT | 14, 14 |
| Le Bas Bernadet (2011) | GTKO/CD55/CD59/CD39/H-transferase | Baboon (n=2) | None | 3, 4 |
| | | Baboon (n=4) | Splenectomy (n=2), CyP, tacrolimus, MMF, CS, C1-INH | 4, 12, 13, 15 |
| Shimizu (2012) | GTKO (MSw) | Baboon (n=2) | ATG, anti-CD2mAb, anti-CD154, MMF, CS | 20–33 |
| | | Baboon (n=1) | As above + thymectomy, splenectomy, TBI | 34 |
| | | Baboon (n=4) | (Vascular thymic lobe or thymokidney) Thymectomy, splenectomy, ATG, anti-CD2mAb, anti-CD154mAb, MMF, CS +/− TBI (n=1) | 56, 68, 81, 83 |
| Pintore (2013) | GTKO/CD55/CD59/CD39/H-transferase | Cynomolgus (n=5) | CyP, CsA, MMF, CS | 18±3.2 (16) |
| | | Cynomolgus (n=3) | Anti-CD20mAb, CsA, MMF, CS | 13±2.3 (12) |
| Spiezia (2013) | CD55 (n=4) | Cynomolgus (n=8) | CyP or anti-CD20mAb, CsA, MMF, CS | 19, 30, 34, 55 |
| | GTKO/CD55 (n=2) | | | 12, 13 |
| | GTKO/CD55/CD59/CD39/H-transferase (n=2) | | | 8, 8 |

Abbreviations (if not used previously):

Anti-CD3IT = anti-CD3 immunotoxin; BSA-Gal = bovine serum albumin conjugated to Gal oligosaccharides; C1-INH = complement component 1 inhibitor; FTY = sphingosine 1-phosphate receptor agonist; vWD = pigs homozygous for von Willebrand disease

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## Table 3

Transplantation of pig livers into NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL – RANGE (MEDIAN) (Hours) |
|---|---|---|---|---|
| Luo (1998) | WT | Baboons (n=2)<br>Rhesus (n=6) | CyP, CsA, CS<br>None (n=3)<br>Cyp, CsA, CS, Dashen (traditional Chinese medicine) (n=3) | <2<br><6 |
| Ramirez (2000) | WT<br>CD55 | Baboon (n=3)<br>Baboon (n=2) | CyP, CsA, CS | <12<br>96,192 |
| Ramirez (2005) | WT<br>CD46/CD59/FT | Baboon (n=4)<br>Baboon (n=5) | Anti-CD25mAb, CyP, anti-CD20mAb, CsA, MMF, CS | <16<br>13–24 (20) |
| Ekser (2010) | WT<br>GTKO<br>GTKO/CD46 | Baboon (n=1)<br>Baboon (n=2)<br>Baboon (n=8) | ATG, CyP, CVF, tacrolimus, MMF, CS | <24<br><24,144<br><24–168 (144) |
| Kim (2012) | GTKO | Baboon (n=3) | ATG, LoCd2b, CVF, anti-CD154mAb, azathioprine, tacrolimus, CS | 72–216 |

Abbreviations as used previously

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## Table 4

Transplantation of pig lungs into NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL (Hours) |
|---|---|---|---|---|
| Daggett (1998) | WT | Baboon (n=7) | Pre-Tx perfusion with pig lungs (n=4), CsA, azathioprine, CS (n=7) | <11 |
| Yeatman (1998) | WT or CD55/CD59 | Baboon (n=10) | CsA, azathioprine, CS +/− CVF | <3 |
| Lau (2000) | CD55/CD59 | Baboon (n=9) | Immunodepletion (3 different methods), CsA, CS, CyP or azathioprine | <24 (details not stated) |
| Gaca (2002) | CD46 | Baboon (n=7) | Immunodepletion, dexamethasone, CsA, CyP, indomethacin, azathioprine +/− anti-human GPIb mAb | <9 |
| Gonzalez-Stawinski (2002) | CD46 | Baboon (n=8; control 4, experimental 4) | Anti-Gal antibody depletion, CsA, CS, CyP or azathioprine, gamma globulin, anti-CD20 mAb, splenectomy | <16 |
| Lau (2003) | vWF-deficient | Baboon (n=5) | CsA, CS, azathioprine | <5 |
| Gaca (2006) | CD46 | Baboon (n=5) | Immunodepletion +/− anti-human C5a mAb (n=3) | <12 |
| Cantu (2007) | WT/macrophage and vWF-deficient | Baboon (n=15) | Immunodepletion | 19–109 |
| Nguyen (2007) | CD46 or GTKO | Baboon (n=6) | CS (details not stated) | <4 |
| Bush (2011) | GTKO/CD55, PIM-depleted (Clodronate liposomes to donor pig) | Baboon (n=2) | CsA, azathioprine, CS | 3–48 |

Abbreviations (if not used previously)

PIM = pulmonary intravascular macrophages

Table 4: References

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## Table 5

Transplantation of pig pancreatic islets in NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (Pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL – RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Söderlund (1999) | WT fetal islet-like cell clusters | Cynomolgus (n=8)<br>Cynomolgus (n=6) | None<br>CsA, 15-deoxyspergualin | <6<br><12 |
| Rijkelijkhuizen (2000a) | WT adult | Cynomolgus (n=4) | CyP, CsA, CS | 4–11 |
| Rijkelijkhuizen (2000b) | WT adult | Cynomolgus (n=4) | CyP, CsA, CS | 4–11 |
| Jonker (2001) | WT adult | Rhesus (n=4) | ATG, CsA, CS, anti-IL2RmAb | 21–53 |
| Buhler (2002) | WT adult<br>WT adult islets + PBPC infusion | Baboon (n=3)<br>Baboon (n=2) | Splenectomy, ATG, CsA, azathioprine<br>Splenectomy, multiple immunoadsorptions, TBI, TI, ATG, CVF, anti-CD154mAb, CsA, MMF, CS | <2<br>12, 28 |
| Cantarovich (2002) | WT adult | Baboon (n=4)<br>Cynomolgus (n=1) | ATG, CsA, MMF, CS<br>ATG, deoxyspergualin, MMF, CS | <2<br><2 |
| Rijkelijkhuizen (2003) | WT adult | Cynomolgus (n=4)<br>Rhesus (n=4) | CyP, CsA, CS<br>ATG, CsA, CS, anti-IL2RmAb | 4–11<br>21–53 |
| Kirchhof (2004) | WT adult | Rhesus (n=6) | None | <1–>3 |
| Elliott (2005a) | WT neonatal | Cynomolgus (n=2) | Encapsulation, nicotinamide | 56 |
| Isaac (2005) | WT neonatal + Sertoli cells | Cynomolgus (n=7) | None | <56 |
| Elliott (2005b) | WT neonatal | Cynomolgus (n=8) | Encapsulation, nicotinamide | >252 |
| Komoda (2005) | WT adult<br>GnT-III adult | Cynomolgus (n=3)<br>Cynomolgus (n=4) | None<br>None | 1–3<br>1–5 |
| Hering (2006) | WT adult | Cynomolgus (n=3)<br>Cynomolgus (n=4)<br>Cynomolgus (n= 5) | Anti-CD25mAb, FTY720, rapamycin<br>Anti-CD25mAb, FTY720, rapamycin, anti-CD154mAb<br>Anti-CD25mAb, FTY720/tacrolimus, rapamycin, anti-CD154mAb, leflunomide | 24–45<br>47–187<br>68–>158 |
| Cardona (2006) | WT neonatal | Rhesus (n=9) | Anti-CD25mAb, anti-CD154mAb, CTLA4Ig (belatacept), rapamycin | 4–>260 (140) |
| Dufrane (2006) | WT adult | Cynomolgus (n=2)<br>Cynomolgus (n=12) | None<br>Encapsulation | <7<br><7–60 (30) |
| Gianello (2007) | WT adult | Cynomolgus (n=4)<br>Cynomolgus (n=4) | Encapsulation, (renal subcapsular)<br>Encapsulation (subcutaneous with islet mono-layer device) | Data not available |
| Rood (2007) | WT and GTKO adult | Cynomolgus (n=2)<br>Cynomolgus (n=4)<br>Cynomolgus (n=4) | ATG, anti-CD20mAb, tacrolimus, rapamycin<br>ATG, CVF, anti-CD154mAb, MMF or rapamycin + tacrolimus<br>ATG, anti-CD154mAb, MMF | <5<br>>58 (partial function)<br>5–7 |
| Cardona (2007) | WT adult | Rhesus (n=5) | Anti-CD25mAb, anti-CD154mAb, CTLA4-Ig (belatacept), rapamycin | 3–76 |
| Rogers (2007) | WT embryonic pancreatic primordia | Rhesus (n=3) | No IS, multiple transplants | 78–409 |
| Casu (2008) | WT adult | Cynomolgus (n=9) | ATG, anti-CD154mAb, MMF | Partial function >60 |
| Garkavenko (2008) | WT neonatal | Cynomolgus (n=12) | No IS | >180 |
| van der Windt (2009) | CD46 adult | Cynomolgus (n=9) | ATG, anti-CD154mAb, MMF | 5–396 (46) |

| FIRST AUTHOR (Year) | DONOR (Pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL – RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Hecht (2009) | Fetal pancreatic fragments | Cynomolgus (n=2) | ATG, anti-CD25mAb, anti-CD20mAb, FTY720, rapamycin, CTLA4-Ig | 280, 380 |
| Igarashi (2010) | WT adult | Cynomolgus (n=4)<br>Cynomolgus (n=5) | Microencapsulation<br>Macrodevice | >42<br>>180 |
| Dufrane (2010) | WT adult | Cynomolgus (n=4)<br>Cynomolgus (n=5) | Microencapsulation<br>Macrodevice | 14<br>136–180 |
| Rogers (2011) | WT embryonic pancreatic primordia<br>WT adult | Rhesus (n=3)<br>Rhesus (n=3) | None<br>None | 56 (Experiments were electively terminated) |
| Thompson (2011a) | WT neonatal | Rhesus (n=9) | Anti–CD25mAb, anti-CD40mAb, rapamycin, CTLA4-Ig (belatacept) | 47–203 (80) |
| Thompson (2011b) | GTKO neonatal (n=5)<br>WT neonatal (n=5) | Rhesus | Anti-CD154mAb, anti-LFA1mAb, MMF, CTLA4-Ig (belatacept) | 50–249 (137) |
| Thompson (2012) | WT neonatal | Rhesus (n=3)<br>Rhesus (n=5)<br>Rhesus (n=5) | MMF, CTLA4-Ig (belatacept), anti-LFA-1mAb, basiliximab<br>MMF, CTLA4-Ig (belatacept), anti-LFA-1mAb, basiliximab, tacrolimus<br>MMF, CTLA4-Ig (belatacept), anti-LFA-1mAb, alefacept, tacrolimus | <50 (none engrafted)<br>46–99<br>92–114 |
| Kim (2013) | WT adult Msw | Rhesus (n=3) | None | <5 |
| Lee (2013) | WT adult | Rhesus (n=2) | Not stated | >120 |
| Vériter (2013) | WT adult | Cynomolgus (n=4)<br>Cynomolgus (n=6) | Coencapsulation with bone marrow-drived stem cells<br>Coencapsulation with adipose-derived stem cells | 1–217<br>14–224 |
| Graham (2013) | WT adult | Cynomolgus (n=not stated)<br>Cynomolgus (n=1) | Various (review of previous data from Hering [2006] and additional data)<br>Anti-CD25mAb, CTLA4-Ig (abatacept), tacrolimus, rapamycin | Various<br>>180 |

Abbreviations (if not used previously):

GnT-III= N-acetylglucosaminyltransferase III

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## Table 6

Transplantation of pig corneas into NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (Pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL - RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Amano (2003) | WT | Cynomolgus (n=6) | None (Stromal disk into stromal pocket) | 60–180 (165) |
| Pan (2007) | WT | Rhesus (n=6)<br>Rhesus (n=4)<br>Rhesus (n=4) | None (PKP)<br>Local betamethasone (PKP)<br>None (ALK) | 12–18 (15)<br>129–276 (183)<br>>90 |
| Li (2011) | WT | Rhesus (n=5)<br>Rhesus (n=5)<br>Rhesus (n=5) | None (ALK, dehydrated)<br>None (ALK, fresh)<br>Local triamcinolone (ALK, dehydrated) | >180<br>>180<br>>180 |
| Choi (2011) | WT | Rhesus (n=5)<br>Rhesus (n=4) | Local prednisone + dexamethasone, systemic CS (ALK, decellularized)<br>Local prednisone + dexamethasone, systemic CS (ALK, fresh) | 195–>391<br>194–>398 |
| Jie (2013) | WT | Rhesus (n=6)<br>Rhesus (n=6) | CYP +bone marrow Tx (PKP)<br>CYP (PKP) | 30–42 (36)<br>12–20 (19) |
| Choi (2013) | PKP allograft, following previous decellularized WT pig ALK | Rhesus (n=5) | Local prednisone + dexamethasone, systemic CS | 35, 49, >324, >379, >421. Previous xeno-sensitization did not influence outcome |

Abbreviations (if not used previously):

ALK = anterior lamellar keratoplasty

PKP = penetrating keratoplasty

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## Table 7

Transplantation of pig artery patches into NHPs (1998–2013)

| FIRST AUTHOR (Year) | DONOR (Pig) | RECIPIENT (n) | IMMUNOSUPRESSIVE THERAPY | SURVIVAL - RANGE (MEDIAN) (Days) |
|---|---|---|---|---|
| Ezzelarab (2012) | GTKO | Baboon (n=3)<br>Baboon (n=5)<br>Baboon (n=1)<br>Baboon (n=1)<br>Baboon (n=4) | No IS<br>Anti-CD154mAb<br>Anti-CD154 mAb, ATG, MMF<br>CTLA4-Ig<br>ATG, MMF, CTLA4-Ig | 14–>28<br>2–>28<br>>28<br>>28<br>14–>28 |

Abbreviations as used previously

Table 7: References

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