Overcoming Coagulation Dysregulation in Pig Solid Organ Transplantation in Nonhuman Primates: Recent Progress

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Abstract: There has recently been considerable progress in the results of pig organ transplantation in nonhuman primates, largely associated with the availability of (i) pigs genetically engineered to overcome coagulation dysregulation, and (ii) novel immunosuppressive agents. The barriers of thrombotic microangiopathy and/or consumptive coagulation were believed to be associated with (i) activation of the graft vascular endothelial cells by a low level of antipig antibody binding and/or complement deposition and/or innate immune cell activity, and (ii) molecular incompatibilities between the nonhuman primate and pig coagulation-anticoagulation systems. The introduction of a human coagulation-regulatory transgene, for example, thrombomodulin, endothelial protein C receptor, into the pig vascular endothelial cells has contributed to preventing a procoagulant state from developing, resulting in a considerable increase in graft survival. In the heterotopic (non–life-supporting) heart transplant model, graft survival has increased from a maximum of 179 days in 2005 to 945 days. After *life-supporting* kidney transplantation, survival has been extended from 90 days in 2004 to 499 days. In view of the more complex coagulation dysfunction seen after pig liver and, particularly, lung transplantation, progress has been less dramatic, but the maximum survival of a pig liver has been increased from 7 days in 2010 to 29 days, and of a pig lung from 4 days in 2007 to 9 days. There is a realistic prospect that the transplantation of a kidney or heart, in combination with a conventional immunosuppressive regimen, will enable long-term recipient survival.

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The pig-to-nonhuman primate (NHP) model has become the standard experimental model in xenotransplantation research.[1-5] Survival of wild-type (ie, genetically unmodified) pig kidneys in NHPs was generally no longer than a few minutes, and the longest life-supporting wild-type kidney graft survival was 22 days in 1998.[4,6]

Genetic modification of the organ-source pig was first reported by Fodor et al[7] in 1994, and Cozzi and White[8] in 1995. Both groups generated pigs expressing human complement-regulatory proteins, CD59[7] and CD55 (decay-accelerating factor),[8] respectively. Transplantation in NHPs of organs from White's CD55 transgenic pigs was associated with prolongation of graft survival (reviewed in Lambrigts et al[6]), with Baldan et al[9] extending pig kidney graft survival to 90 days in 2004. The introduction of costimulation blockade by Bühler et al[10] largely resolved the problem of the adaptive immune response, inhibiting the production of de novo anti-pig antibodies. The availability of α1,3-galactosyltransferase gene-knockout (GTKO) pigs, produced in 2003 by Phelps et al[11] and in 2004 by Kolber-Simonds et al,[12] extended pig heart graft survival in baboons to 179 days.[13] The combination of GTKO and expression of a human complement-regulatory protein extended survival further.[14]

However, the barriers of thrombotic microangiopathy and/or consumptive coagulation then became more obvious.[15,16] These complications were believed to be associated with (i) low-grade activation of the graft vascular endothelial cells (VECs) by a low level of anti-pig (non-Gal) antibody binding and/or complement deposition and/or innate immune cell activity, and (ii) molecular incompatibilities between the NHP and pig coagulation-anticoagulation systems.[17,18] The activated VECs became procoagulant, and this could not be successfully controlled by the pig's anticoagulant factors. The introduction of a human coagulation-regulatory transgene, for example, thrombomodulin, endothelial

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protein C receptor, into the NHP VECs, contributed greatly to preventing a procoagulant state from developing.

These genetic manipulations,[19-25] coupled with improvements in the immunosuppressive regimens used, resulted in further progress in pig-to-NHP organ transplant models. It is this progress that we review here.

HEART

Considerable progress has been made in the pig-to-NHP heterotopic (non–life-supporting) heart xenotransplantation model but, before clinical trials can take place,[26,27] this needs to be duplicated (at least to some extent) in the orthotopic (life-supporting) heart transplant model.

Heterotopic (Abdominal) Pig Heart Xenotransplantation

A benchmark was set by Kuwaki et al[13] in 2005 when, by transplanting hearts from the first GTKO pigs that became available, graft survival of 179 days was achieved (Table 1A, Figure 1). Extensive thrombotic microangiopathy developed in the graft, leading to consumptive coagulopathy in the recipient. The experiment was also problematic because an anti-CD154 monoclonal antibody (mAb), which formed the basis of the immunosuppressive regimen, had been found to have thrombogenic properties.[40,41] Whether the agent contributed to the thrombotic microangiopathy remains unknown, but probably did not because thrombotic

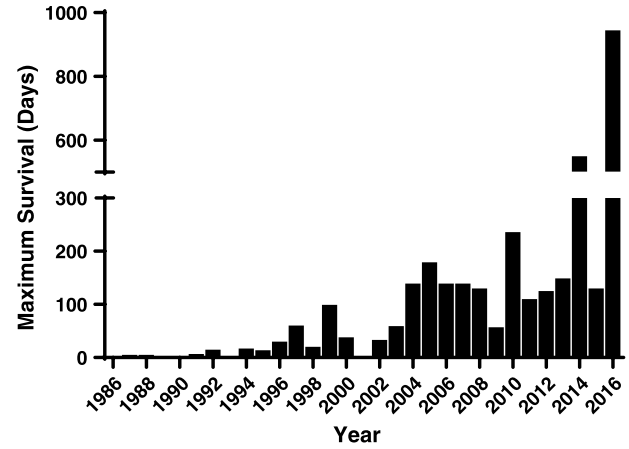

FIGURE 1. In heterotopic heart xenotransplantation, maximum survival has been improved from <8 hours in 1986 to 945 days.

TABLE 1.

Recent progress in pig-to-NHP heart xenotransplantation

Year	Recipient	Donor (pig)	Therapeutic regimen	Longest survivals (days)	References
(A) Abdominal heterotopic heart xenotransplantation					
2005	Baboon	GTKO	ATG, thymic irradiation, LoCD2b, anti-CD154mAb, MMF, CS, CVF	56, 67, 78, 110, 179 (n = 8)	13
2012	Baboon	GTKO/CD46	ATG, anti-CD20mAb, anti-CD154mAb, MMF, CS, CVF	75, 115, 179, 236 (n = 11)	28
2014	Baboon	GTKO/CD46	ATG, anti-CD20mAb, anti-CD40mAb, MMF, CS, CVF	60, 107, 147, 149 (n = 9)	29
2015	Baboon	GTKO/CD46	ATG, anti-CD20mAb, +/–anti-CD154mAb, MMF, CS, CVF, CTLA4-Ig, +/–rapamycin, +/–tacrolimus	33, 52, 99, 130 (n = 7)	30
2014, 2016	Baboon	GTKO/CD46/TBM	ATG, anti-CD20mAb, anti-CD40mAb, MMF, CS, CVF	146, 550, 616, 945 (n = 9)	31-33
(B) Orthotopic heart xenotransplantation					
2000	Baboon	CD55	CyP, CsA, MMF, CS	39 (n = 1)	34
2005	Baboon	CD55	CyP, CsA, MMF, CS	<1,12,14, 20 (n = 4)	35
2005	Baboon	CD55	ATG, GAS914, tacrolimus, sirolimus, CS, anti-CD20mAb, +/–Cyp	1, 1, 9, 25 (n = 4)	36
2011	Baboon	CD46	ATG, anti-CD20mAb, αGal-polymer, tacrolimus, sirolimus, CS,	57, 40, 34 (n = 10)	37
(C) Intrathoracic heterotopic heart xenotransplantation					
2010	Baboon	GTKO/CD46	Immunoabsorption, ATG, anti-CD20mAb, tacrolimus, sirolimus, MMF, CS, IVIG, bortezomib	<1, 50 (n = 2)	38
2015	Baboon	GTKO/CD46	Immunoabsorption, ATG, anti-CD20mAb, tacrolimus, MMF, CS,+/–bortezomib, +/–CyP	17, 18, 19, 50 (n = 14)	39
		GTKO/CD46/TBM	Immunoabsorption, ATG, anti-CD20mAb, tacrolimus, MMF, CS,+/–bortezomib, +/–CyP	17, 18, 19 (n = 6)	
		GTKO/CD46/HLA-E	Immunoabsorption, bortezomib, CyP, ATG, anti-CD20mAb, tacrolimus, MMF, CS	35 (n = 1)	

ATG, antilymphocyte globulin; CS, corticosteroid; CsA, cyclosporine A; CVF, cobra venom factor; CyP, cyclophosphamide; GAS914, Gala(1,3)Gal trisaccharidepolylysine; LoCD2, anti-CD2mAb; MMF, mycophenolate mofetil.

microangiopathy can clearly occur when this agent is not being administered.

In 2012, graft survival was increased to 236 days by adding a B cell–depleting agent (anti-CD20mAb) to the induction regimen (previously advocated by McGregor and his colleagues,[42] but the maintenance regimen remained based on an anti-CD154mAb (Table 1).[28] After replacing the anti-CD154mAb with an anti-CD40mAb, and, importantly, by adding a human coagulation-regulatory protein (thrombomodulin) on to the pig's GTKO/CD46 background, the same group extended graft survival beyond 1 year (to 550 days), a milestone in the progress in xenotransplantation research (Table 1).[31,32] In 2016, a further significant prolongation of graft survival to 945 days was achieved, using the same source pig and the same immunosuppressive regimen (Table 1, Figure 1).[33]

Encouraging results were also obtained by our own group,[30] but without the extremely long graft survival reported by Mohiuddin and his colleagues. The discrepancy in these results may possibly be explained by the facts that (i) at that time, we did not include a B cell–depleting agent in our regimen, and (ii) Mohiuddin maintained a continuous intravenous infusion of heparin throughout the experiment, which would clearly not be ideal for clinical application. Mohiuddin's regimen, therefore, requires some modifications before it would be applicable to clinical use. It will also be necessary to reproduce these encouraging results in an orthotopic, life-supporting model.

Life-supporting Orthotopic and Partial Life-supporting Intrathoracic Heterotopic Heart Xenotransplantation

There have been relatively few life-supporting pig orthotopic heart xenotransplants carried out in NHPs in recent years.[35,36,43-50] A benchmark was set by Vial et al[34] in 2000 when survival of 39 days was reported, using a CD55 transgenic pig heart (Table 1B). Byrne et al[37] extended this survival to 57 days, using a pig transgenic for CD46 and, in the absence of GTKO, with the infusion of a Gal-polymer (to block anti-Gal antibody) (Table 1B).[42] However, this group (and others) experienced a high early failure from a condition they have termed "perioperative cardiac xenograft dysfunction."[51] The exact reasons for this remain uncertain, but (i) technical problems, (ii) ischemia-reperfusion injury, and perhaps (ii) the impact of early antibody binding and complement activation (though insufficient to cause rejection) may be playing roles.[51] However, a significant fall in thyroid hormones, particularly in free triiodothyronine (fT3), which occurs during cardiopulmonary bypass[52-56] and also after any xenotransplant procedure,[57,58] and is associated with a reduction in myocardial energy stores,[59] may be a major causative factor. Exploration of this possibility is certainly indicated (recently, however, survival after orthotopic heart transplantation has been extended to 90 days [Reichart B, oral communication, September 2017]).

Survival after partial life-supporting intrathoracic heterotopic heart transplantation has also been limited, probably for the same reasons, with maximal survival of 50 days (Table 1C).[38,39]

In summary, the addition of a human coagulation-regulatory protein, for example, thrombomodulin,[60] to the pig would appear to have largely overcome the combined barrier of thrombotic microangiopathy and consumptive coagulopathy, facilitating prolongation of graft survival. B cell depletion may also have contributed to the improved outcome. We suggest that studies should aim for *consistent* survival (eg, 5 of 6 experiments) of a NHP with a life-supporting pig heart for periods of at least 3 months (or possibly 6 months) with (i) a clinically applicable immunosuppressive regimen, and an absence of (ii) major life-threatening complications (eg, infections) and of (iii) histopathological features of antibody-mediated or cellular rejection and/or thrombotic microangiopathy.

KIDNEY

By 2004, CD55 kidney graft survival had been extended to 90 days in cynomolgus monkeys (Table 2, Figure 2).[9] GTKO pig kidney graft survival reached 83 days in 2005 (with cotransplantation of donor-specific thymic tissue) (Table 2).[61] Thereafter, pig kidney transplantation in NHPs showed only slow improvement until 2015 (Figure 2).

Higginbotham et al[67] reported kidney recipient survival of greater than 122 and greater than 130 days (both monkeys ongoing at the time of the report) after the transplantation of GTKO/CD55 pig kidneys in rhesus monkeys selected for their low titers of antipig antibodies (Table 2). The immunosuppressive regimen differed to some extent from that used by most other groups, but was still based on

TABLE 2.

Recent progress in pig-to-NHP kidney xenotransplantation

Year	Recipient	Donor (pig)	Therapeutic regimen	Longest survivals (days)	References
2004	Cynomolgus monkey	CD55	CyP, CsA, MMF, CS	20, 40, 48, 90 (n = 7)	9
2005	Baboon	GTKO	ATG, LoCD2b, anti-CD154mAb, MMF, CS, +/−CVF	31, 56, 68, 81, 83 (n = 14)	61
2015	Baboon	GTKO/CD46/CD55/TBM/EPCR/CD39	ATG, anti-CD20mAb, anti-CD40mAb, rapamycin, CS, +/−CVF	136 (n = 1)	62
2016	Rhesus monkey	GTKO/CD55	anti-CD4mAb, anti-CD8mAb, anti-CD154mAb, MMF, CS	160, 310 (n = 5)	63
2017	Baboon	GTKO/CD46/CD55/EPCR/TFPI/CD47	ATG, anti-CD20mAb, anti-CD40mAb, rapamycin, CS, +/−CVF	237, 260 (n = 4)	64
2017	Rhesus monkey	GTKO/CD55	anti-CD4mAb, anti-CD154mAb, MMF, CS	499 (n = 10)	65
2017	Rhesus monkey	GTKO/β4GalNT2-KO	anti-CD4mAb, anti-CD8mAb, anti-CD154mAb, MMF, CS	435 (n = 2)	66

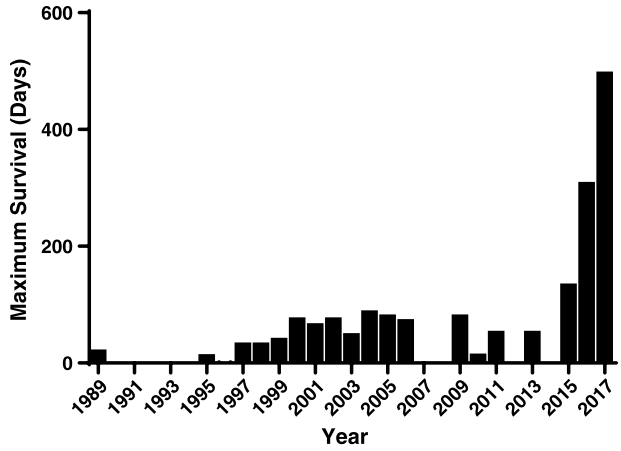

FIGURE 2. In kidney xenotransplantation, maximum survival has been significantly improved from 23 days in 1989 to >1 year. The longest survival was reported 499 days in 2017.

costimulation blockade (with anti-CD154mAb). These 2 monkeys were followed further, the grafts failing at 160 and 310 days, respectively, with histopathological features of acute humoral xenograft rejection (Table 2, Figure 2).[63]

The Higginbotham study is important not only for achieving prolonged graft survival but also for drawing attention to the role played by anti-pig antibody in that survival. Using the same pig source and an identical immunosuppressive regimen, a monkey with a high level of anti-pig (non-Gal) antibodies rejected its graft within 6 days, indicating the importance of antibody to the outcome. This observation follows similar observations (though not followed up) by Kuwaki et al[13] in 2005, who had selected NHPs with low antipig (non-Gal) antibody levels to offer an advantage.

From the same group as Higginbotham, Kim et al[65] reported 499 days survival of a pig kidney graft (Table 2, Figure 2). Furthermore, using the same immunosuppressive regimen as Higginbotham, Martens et al[66] reported kidney graft survival of >400 days in a rhesus monkey when the kidney was taken from a GTKO/β4GalNT2-KO pig (that did not express either Gal or Sda) (Table 2, Figure 2). No human complement- or coagulation-regulatory proteins were expressed in the pig.

Our own group has reported prolonged survival of a kidney grafts from pigs with multiple genetic modifications that included 2 human coagulation-regulatory transgenes (Table 2). One functioned in a baboon (with a high titer of anti-pig IgM) for 136 days, before having to be euthanized for a rare systemic infection.[62] Two others remained healthy for 237 and 260 days, respectively, when again infectious complications led to termination of the experiments (Table 2).[64] Biopsies in all 3 kidneys showed normal histology. Renal graft function remained normal with minimal proteinuria with no accompanying hypoalbuminemia. There were no or minimal features of a consumptive coagulopathy.

The importance of the expression of a human coagulation-regulatory protein is emphasized by the observation that 2 other baboons, treated identically to those above, but with very poor expression of a coagulation-regulatory protein (human thrombomodulin) in the kidneys, required euthanasia after 12 days for the development of a consumptive coagulopathy (Table 2).[64] The difference in outcome between these 2 baboons (with pig kidneys *not* expressing an effective human coagulation-regulatory protein) and the 2 summarized above (with pig kidneys expressing 2 effective human coagulation-regulatory proteins) is remarkable, and provides support for the importance of expression of these proteins in this model.

However, it is of considerable interest to note that the pig kidneys transplanted into rhesus monkeys by Higginbotham and colleagues did *not* express a human coagulation-regulatory protein, and also the immunosuppressive regimen included the "thrombogenic" anti-CD154mAb. Furthermore, heparin was not administered to these monkeys. It is perhaps remarkable that neither a thrombotic microangiopathy nor a consumptive coagulopathy developed in either of these monkeys, suggesting that there may be biological differences between monkey and baboon. Whether a *human* recipient would be anticipated to be more comparable to the baboon or rhesus monkey in this regard is uncertain. However, other subtle differences in the immunosuppressive regimen may have influenced the outcome (Table 2).

The significant progress in pig kidney transplantation in *baboons* (though not in rhesus monkeys) has been achieved to a significant extent because of the protection of the pig tissues from the primate immune response and from coagulation dysregulation provided by the genetic manipulation of the pig.[11,68,69] Effective immunosuppressive therapy and anti-inflammatory therapy in the form of tocilizumab (Table 2) almost certainly contributed to the good outcome (tocilizumab has significant effects on the immune system).[70] In rhesus monkeys, however, the expression of either a human complement- or coagulation-regulatory protein would seem to be unnecessary. The differences between these 2 NHP species require further investigation.

LIVER

The rapid development (within minutes) of profound thrombocytopenia reported by Ekser et al[71-74] after orthotopic GTKO or GTKO/CD46 pig liver transplantation in baboons

TABLE 3.

Recent progress in pig-to-NHP liver xenotransplantation

Year	Recipient	Donor (pig)	Therapeutic regimen	Longest survivals, d	References
2010	Baboon	GTKO, GTKO/CD46	ATG, tacrolimus, MMF, CS, +/– CVF	4, 5, 6, 7 (n = 10)	75
2012	Baboon	GTKO	ATG, anti-CD154mAb, +/–Azathioprine, +/–LoCd2b, tacrolimus, CS, Aminocaproic acid, CVF	5, 8, 9 (n = 3)	74
2016	Baboon	GTKO	ATG, belatacept, tacrolimus, CS, CVF, hPCC	25 (n = 1)	76
2017	Baboon	GTKO	ATG, anti-CD40mAb or belatacept, tacrolimus, CS, CVF, hPCC	5, 8, 25, 29 (n = 4)	77

hPCC, human prothrombin concentrate complex.

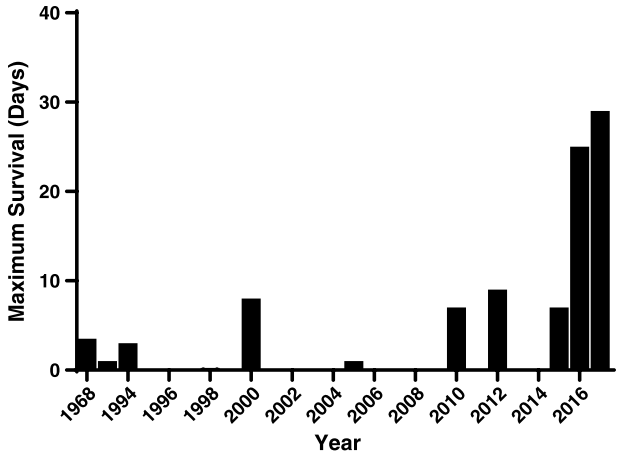

FIGURE 3. Only few data related to liver xenotransplantation have been reported, with the longest survival being 29 days.

was problematic and formed a basis for further studies (Table 3, Figure 3). Apart from this major complication, pig hepatic function appeared to be quite good (for up to 7 or 8 days),[75,78,79] and so subsequent studies have been directed toward resolving this problem.[80]

A major factor would appear to be incompatibilities of cell surface receptor-ligand interactions between pig endothelial cells and primate platelets[81,82] or the presence of natural antibodies to pig liver endothelial antigens, leading to endothelial cell activation.[81,82]

In vitro and in vivo studies suggested potential factors in the causation of thrombocytopenia and dysregulation of coagulation to be (i) asialoglycoprotein receptor 1 (ASGR1) involvement in xenogeneic platelet phagocytosis (seen in vitro and in a pig-to-human ex vivo perfusion model),[83] and (ii) incompatibilities between species (eg, CD47/signal-regulatory protein alpha, CD18, macrophage antigen complex-1, von Willebrand Factor [vWF]/GPIb).[82,84]

Subsequently, Kim et al[74] achieved 9 days of survival using a GTKO pig liver (Table 3, Figure 3). The administration of aminocaproic acid (amicar) resulted in the partial resolution of thrombocytopenia, maintaining platelet counts greater than 40000/mm^3 throughout the study. However, the recipient died from bleeding and enterococcal infection, though there was no evidence of rejection.

Most recently, Shah et al[77] reported 25 and 29 days of life-supporting orthotopic GTKO pig liver xenograft survival with stable hepatic function (demonstrated by the production of porcine proteins and coagulation factors), using a continuous infusion of human prothrombin concentrate complex (exogenous human coagulation factor, human Factor VIIa) (Table 3). The baboons were euthanized because of plantar ulcerations and deteriorating liver function.

In summary, disturbances of coagulation were again at the core of survival of pig liver graft recipients, though these disturbances varied to some extent from those seen after heart and kidney xenotransplantation, requiring different genetic modifications of the source pig, for example, expression of human CD47, ASGR-KO. Treatment of the recipient with coagulation factors is less than ideal, and more effort needs to be directed to correct the deficiencies by genetic engineering. Nevertheless, an extension of graft survival to almost 1 month (in the absence of rejection) indicates that progress is being made.

Because there is no support available to patients in fulminant or severe hepatic failure (comparable to dialysis or a ventricular assist device), survival of a pig graft may not need to be for more than a few days or weeks to be considered for clinical application as a bridge to allotransplantation.[85] Nevertheless, there has to be conclusive evidence from preclinical models that the treatment necessary to maintain the xenograft will not be detrimental to the outcome of the subsequent allograft.

LUNG

Donor shortage is problematic across all organ transplants, but lungs have the lowest harvest rates,[86] increasing the need for an alternative source. Even lung *allografts* are highly sensitive to injury and to multiple immune rejection mechanisms,[87,88] rendering the barrier to lung *xenotransplantation*, particularly high, and certainly higher than to other vital organs.[89]

Several experimental models have been established to study lung xenotransplantation.[90,91] Most studies have employed ex vivo pig lung perfusion with human blood,[92,93] but unilateral pig lung transplantation in baboons is also being carried out (Table 4). A complex interaction of inflammation, coagulation, and tissue injury leads to relatively rapid lung xenograft failure, both ex vivo during perfusion with human blood and after transplantation into a NHP. This is illustrated by the observation that, during the past 2 decades, life-supporting pig lung xenograft survival in NHPs has been extended only from 11 hours[97] to 9 days (Table 4).[95,96]

TABLE 4.

Recent progress in pig-to-NHP lung xenotransplantation

Year	Recipient	Donor (pig)	Therapeutic regimen	Longest survivals	References
2007	Baboon	GTKO	C1 esterase inhibitor, 1-benzylimidazole (thromboxane synthase inhibitor), histamine receptor blockade, CS	4 h	94
2015	Baboon	GTKO/CD46/CD55/EPCR/TFPI/CD47	C1 esterase inhibitor, 1-benzylimidazole (thromboxane synthase inhibitor), histamine receptor blockade, anti-GPIb mAb, CS	8 d	95
2017	Baboon	GTKO/CD46/vWF OR GTKO/CD46/CD47/HO-1/EPCR/TBM OR GTKO/CD46/CD47/CD55/EPCR/TFPI	ATG, anti-CD20mAb, C1 esterase inhibitor, thromboxane synthase inhibitor, histamine receptor blockers, anti-GPIb Fab, MMF, tacrolimus (OR anti-CD40mAb), anti-IL6R, α1-antitrypsin, CS	7-9 d	96

TABLE 5.

Pharmacological therapy tested in lung xenotransplantation

Agents	Effect	References
To Recipient		
1-benzylimidazole	Thromboxane synthase inhibition	96,109,110, (submitted to JHLT)
AAT	Inhibition of proteases released by inflammatory cells, especially neutrophils	111
Complement fragment 1 esterase inhibition	Complement inhibitor	112
Diphenhydramine, famotidine	Histamine receptor blockade	96,113, (submitted to JHLT)
GPIb mAb blockade	Inhibition of platelet adhesion	113-115
GPIIb/IIIa blockade	Inhibition of platelet aggregation	113-115
To Donor		
Liposomal clodronate	Depletion of pig pulmonary macrophages	106
Desmopressin	Depletion of pig vWF from endothelium	112,113

AAT, Alpha-1-antitrypsin.

In ex vivo perfusion models, using human blood, with monitoring for 4 to 8 hours, the following have been identified as being beneficial to lung function and survival: (i) expression of a human complement-regulatory protein, for example, hCD46,[98] or (ii) HLA-E[99] or (iii) knockout of N-glycolylneuraminic acid.[68,100] A meta-analysis of multiple genetic modifications on pig lung xenografts[101] found that expression of the inflammation-regulatory protein HO-1 or human endothelial protein C receptor, but not human thrombomodulin or hCD39 were associated with further beneficial effects on the outcome.

In xenotransplantation models, some reports indicate that certain genetic modifications prolong pig lung survival, for example, (i) GTKO,[94] (ii) the addition of a human complement-regulatory protein, such as hCD46[89,98,101,102] and hCD55/hCD59[97,103] or (iii) expression of a human coagulation-regulatory protein, for example, human endothelial protein C receptor,[95,104] human tissue factor pathway inhibitor[95,105] or (iv) transgenic expression of hCD47.[95,106,107]

Pig vWF plays a role in "delayed" (24 hours) dysfunction in pulmonary xenotransplantation,[106] and it has been suggested that the replacement of pig vWF with human vWF will help overcome hypercoagulability.[108]

As each individual genetic manipulation has been demonstrated to have only a limited effect, multigene-modified pigs will be necessary to achieve a clinically meaningful lung xenograft outcome. Pierson's group have accomplished survival beyond 1 week with life-sustaining function using a "multigene" pig lung (Table 4). Normal lung function and histology was documented for several days.[95]

Pharmacological treatments (to recipient NHP and/or donor pig), targeting various known aspects of xenorejection mechanisms, including inflammation and coagulation pathways, have been shown to be effective and may prove to be essential to protect a xenogeneic lung graft after transplantation (Table 5).[94,106,109-119]

In summary, although significant progress has been made in pulmonary xenotransplantation, the barriers remain considerable. As with other solid organs, coagulation dysregulation has been identified as one of the major hurdles to be overcome, possibly representing, due to the structure and anatomy of the lung, an even greater problem in xeno lung transplantation than observed with other organs. Further exploration, involving new donor transgenes or transgene combinations and targeted drug treatments will be required to further advance pulmonary xenotransplantation toward clinical applications.

COMMENT

In the past several years, the survival of pig kidneys and hearts in NHPs has been significantly prolonged through the transplantation of organs from genetically engineered pigs and the administration of novel immunosuppressive therapy. Progress has been sufficiently encouraging for groups in the United States to begin to consider approaching the Food and Drug Administration to discuss potential clinical trials of pig kidney transplantation.[120] The survival of pig livers and lungs has been limited and requires further genetic modification of the source pig.

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