Article DOI: http://doi.org/10.3201/eid3007.240273

Infectious Diseases and Clinical Xenotransplantation

Appendix

Appendix Table 1. Potential targets for genetic manipulation in swine xenograft donors

Target type	Target	Potential gene targets for xenotransplantation
Pig breed	—	Various pig breeds
Endogenous retrovirus Inactivation	Virus	Porcine endogenous retrovirus (PERV A, B, C, AC)
Knockout	Carbohydrate antigens	GGAT1 (α-1,3-glycosyltransferase)
	Carbohydrate antigens	B4GalNT2 (glycosyltransferase)
	Carbohydrate antigens	CMAH (cytidine monophosphate-N-acetylneuraminic acid hydroxylase)
	Organ growth	Growth hormone receptor
Added human transgenes	Complement regulation	CD46 (hMCP, human membrane cofactor protein)
	Complement regulation	CD55 (hDAF human decay-accelerating factor)
	Coagulation	THBD (human thrombomodulin gene)
	Coagulation	EPCR (Endothelial cell protein C receptor)
	Innate immunity	CD47 (Block SIRPα tyrosine phosphorylation)
	Inflammation, apoptosis	HO1 (Heme Oxygenase-1)
	Inflammation, apoptosis	HA20 (Human A20)

Appendix Table 2. Risk categories for potential pathogens in recipients of porcine xenografts (*1*,*2*)*

Organism hosts	Examples	Microbiologic assays available?	Monitor in breeding colony?
Pathogens of immunologically normal humans and swine	Influenza viruses* (*3*–*6*); Hepatitis E virus* (*7*–*9*); *Mycobacterium tuberculosis**; rabies*; many bacterial and parasitic species (e.g., Ascaris, Toxocara, Pasteurella multocida; Mycoplasma spp.)	Yes	Yes
Known pathogens of immunosuppressed human transplant recipients	*Toxoplasma gondii**; *Strongyloides* spp.*; *Aspergillus sp.; Cryptococcus spp; Cryptosporidium spp.*	Yes	Based on risk with organism
Porcine organisms similar to common pathogens of immunosuppressed human transplant recipients	Porcine adenovirus; porcine parvovirus 1; porcine respiratory coronavirus; parainfluenza virus 3	Few	Require validation of assays in human blood or tissues.
Unique swine pathogens (may replicate only in pig cells)	Porcine cytomegalovirus (PCMV)* (*14*–*18*); Porcine circovirus (PCV 1–4) (*19*–*24*); porcine lymphotropic herpesvirus (PLHV 1,2); porcine endogenous retrovirus* (PERV A, B, C, AC) (*1*,*25*)	Some	Herpesviruses generally species-specific. Risk requires clinical study
Organisms routinely tested for health status of swine	Porcine enterovirus spp; *Lawsonia Intracellularis;* porcine epidemic diarrhea virus;transmissible gastroenteritis virus; porcine delta coronavirus; *Brucella suis*; porcine reproductive and respiratory syndrome virus; porcine epidemic diarrhea virus;*Pseudorabies* virus	Yes	Yes

Organism hosts	Examples	Microbiologic assays available?	Monitor in breeding colony?
Porcine organisms largely geographically restricted (*4*,*26*,*27*) (examples)	*Burkholderia pseudomallei*; *Clonorchis sinensis; Echinococcus* spp; *Schistosoma* spp; African swine fever (ASF) virus; Menangle virus; Nipah virus (*28*,*29*); porcine circovirus type 4 (PCV4)	Some	Monitor for future geographic spread

*Consider exclusion of infected animals carrying these species. PERV may be excluded genetically (e.g., CRISPR-cas9) ; PERV-C negative animals carry potentially infectious PERV-A and B.

Appendix Table 3. Considerations in routine testing of xenograft recipients*

Virus	Testing method
Porcine endogenous retrovirus (PERV) A, B, C, AC (if present in source animal) +	Qualitative and quantitative (QNAT) nucleic acid testing (NAT); antibody- based tests (serology, ELISA, Western Bylot)+
Porcine lymphotropic herpesvirus type 2 (PLHV-1–2)	QNAT+
Porcine circovirus (PCV 1–4)	QNAT
Porcine cytomegalovirus (PCMV)	NAT+; serology
Human cytomegalovirus (HCMV) – per risk status	QNAT, serology
Human Epstein-Barr virus (EBV) – per risk status	QNAT, serology
BK polyomavirus (kidney recipients) – per protocol	QNAT
Pig cell chimerism in circulation (PBMC)	QNAT+ (e.g., P-MHC class I gene; p-mtCOII gene) in recipient PBMC DNA.
Unknown pathogens	Metagenomics or next generation sequencing (*10*–*13*)

* Additional testing is needed for individuals with infectious syndromes. QNAT: quantitative nucleic acid test; P-MHC: porcine major histocompatibility complex; p-mtCOII: pig mitochondrial cytochrome *c* oxidase subunit II gene
+ Quantitative NAT for PERV and other viruses must be normalized against chimerism studies to correct for the number of circulating pig cells in blood samples.

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