

Theme issue on infections and safety—An introduction

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DNA viruses, herpes viruses, islet cell xenotransplantation, RNA viruses, solid organ xenotransplantation, virus safety

Welcome to the first issue dedicated to safety and infectious risk. Xenotransplantation using pig cells, tissues, and organ has made enormous progress in the recent years. This included the generation of multiple genetically modified animals and more effective immunosuppression regimens, leading to an remarkable survival time of the transplants in non-human primates (NHP) as well as an improved screening for and elimination of potential zoonotic porcine microorganisms. In this collection of manuscripts, several aspects of safety research in the xenotransplantation field will be reviewed and original papers are added to give a broad overview about the state of art of prevention of transmission of porcine microorganisms, first of all porcine viruses.

In the paper related to this issue, Robin Weiss, who first described the infection of human cells by porcine endogenous retroviruses (PERVs), gives a short historical overview from the very beginning of xenotransplantation.¹ In this contribution, as well as in others,^{2,3} not only PERVs were recognized as potential zoonotic pathogens, but also numerous other porcine RNA and DNA viruses. As reported here, lessons can be learned from allotransplantation and vice versa.²

Alternatives to xenotransplantation such as the use of pig stem cells are also reported in this issue⁴; however, stem cells were characterized by an elevated expression of PERVs. These studies implicate that when transplanting a pig organ which contains stem cells in low concentration, not detectable by sensitive detection methods, the recipient may nevertheless be at risk of infection due to the high local release of PERV. Fiebig et al⁵ used a new, most effective method, droplet digital polymerase chain reactions (ddPCRs), to assess for PERV copy number and found differences in different organs of a single pig. This is an important consideration with respect to the tissue being utilized. Indeed, this has been previously observed and is now confirmed.^{6,7} Noordergraaf et al⁸ provide important lessons when populating a source animal facility, especially in their contamination with circovirus. Further information is reported by Egerer et al,⁹ demonstrating the elimination of porcine cytomegalovirus

(PCMV) by early weaning prior to the settlement of a new pig facility. Hartline et al¹⁰ used a panel of 30 diagnostic PCR to screen pigs derived by cesarean section. Nevertheless, they still detected mycoplasma species in these piglets, but no porcine lymphotropic herpesviruses 2 and 3, which had been found in the mother sows.

One related issue is the question as to whether we can fully evaluate the risk posed by PERV and other viruses. It is clear in this issue that careful monitoring and the use of sensitive diagnostics are key, but it may not be possible to evaluate the full risk until we move to the clinic.^{11,12} Inactivation of genomic PERV by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas may be a solution to ban the risk of transmission of PERV.^{13,14} However, in all previous pre-clinical (well knowing that non-human primates are far from suitable models) and clinical xenotransplantations, no PERV has been transmitted.^{12,15,16} In addition, the influence of CRISPR/Cas on the pig genome is still not well analyzed; for example, off-target effects by CRISPR/Cas9 or suppression of p53 and enhanced oncogenicity have not been studied.^{11,17–19} At present, and for scientific reasons discussed previously and in the articles in this issue^{11,16} as well as above, it seems possible to move to the clinic using animals without PERV inactivation. We would like to thank all contributing authors who prepared the manuscripts in a relatively short period after we invited them as well as the reviewers, the Associate Editor and the Editor-in-chief for supporting this theme issue. We hope that you enjoy this issue and look forward to further discussion.

CONFLICT OF INTEREST

JD and LS have no conflict of interests.

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