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Emerging Trends in Xenotransplantation

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Abstract—*Organ failure is one of the prominent causes of mortality in modern world. The remedy is transplantation of the organs from willing healthy and suitable donors. Sadly, there is a dearth of organ donors for the life saving organs. It has been a long standing ambition of the scientific community to develop a technology that would enable the development of organs in animals that could be transplanted into humans without complications. Pigs have been identified as the animals of choice because of similar size, anatomy and functioning of organs. Regrettably, past experiments have failed miserably due to the complications arising from immune reactions, viral infections and ethical constraints of the experiments.*

Interestingly, the xenotransplantation has breathed a new life due to development of new generation of immune suppressants and genome editing technology such as CRISPER/CAS9. These techniques efficiently edit pig genome and can be used to edit the pig genes that could cause rejection or infection. Cascade of immune mechanisms such as acute rejection, acute humoral rejection and immune cell mediated rejection have proven to be insurmountable barriers for the xenotransplantation A formidable challenge for pig to human transplantation is the presence of porcine endogenous retrovirus (PERV) in pig cells. PERV can integrate into the human genome causing dangerous disease. Yang et al. 2015 described the eradication of all PERVs in a porcine kidney epithelial cell line (PK15) using CRISPR/Cas9 and demonstrated a >1000 reduction in PERV transmission.

The most profound barrier to pig-to-primate xenotransplantation is the rejection of the grafted organ by a cascade of immune mechanisms commonly referred to as hyperacute rejection (HAR), acute humoral xenograft rejection (AHXR), immune cell-mediated rejection, and chronic rejection. Various strategies for the genetic modification of pigs facilitate tailoring them to be donors for organ transplantation. Genetically modified pigs lacking alpha-1,3-Gal epitopes, the major xenoantigens triggering HAR of pig-to-primate xenografts, are considered to be the basis for further genetic modifications that can address other rejection mechanisms and incompatibilities between the porcine and primate blood coagulation systems. These modifications include expression of human complement regulatory proteins, CD39, endothelial protein C receptor, heme oxygenase 1, thrombomodulin, tissue factor pathway inhibitor as well as modulators of the cellular immune system such as human TNF alpha-related apoptosis inducing ligand, HLA-E/beta-2-microglobulin, and CTLA-4Ig.

Keywords*: xenotransplantation, organ failure, PERV, CRISPR/Cas9*