Frankenswine or bringing home the bacon: how close are we to clinical trials of xenotransplantation?

Abstract: The results of organ and cell allotransplantation continue to improve, but the field remains limited by a lack of deceased donor organs. This problem might be resolved by the transplantation of organs from pigs genetically-engineered to protect them from the human immune response.

The pathobiological barriers to successful pig organ transplantation in primates include activation of the innate and adaptive immune systems, coagulation dysregulation, and inflammation. The transplantation of organs and cells from pigs that do not express the important Gal antigen (α1,3-galactosyltransferase gene-knockout [GTKO] pigs) and express one or more human complement-regulatory proteins (hCRP, e.g., CD46, CD55), when combined with an effective T cell costimulation blockade-based immunosuppressive regimen, prevents early antibody-mediated and cellular rejection.

However, low levels of anti-nonGal antibody and innate immune cells and/or platelets may initiate the development of a thrombotic microangiopathy in the graft that may be associated with a consumptive coagulopathy in the recipient. This pathogenic process is accentuated by the dysregulation of the coagulation-anticoagulation systems between pigs and primates. The expression in GTKO/hCRP pigs of a human coagulation-regulatory protein, e.g., thrombomodulin, is increasingly being associated with prolonged pig graft survival in nonhuman primates.

Genetic engineering of the organ-source pig, combined with novel immunosuppressive therapy, has increased pig heart, kidney, islet and corneal graft survival in nonhuman primates from minutes to months or even years. Genetic engineering may also contribute to any physiological barriers that might be identified as well as to reducing the risks of transfer of a potentially infectious microorganism with the organ.

There are now an estimated 30 or more genetic manipulations that have been carried out in pigs, with some pigs expressing 5 or 6 manipulations. With the new technology now available, it will become increasingly common for a pig to express even more genetic modifications, and these could be tested in pig-to-nonhuman primate models to assess their efficacy and benefit.

Initial clinical trials of islet and corneal xenotransplantation are already underway, and trials of pig kidney or heart transplantation are firmly anticipated within the next five years.