Genetically engineered pigs: Advance looks promising

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A domestic pig on an organic farm in Solothurn, Switzerland. Image: Wikimedia Commons

Stories of people waiting for organ transplants that could save their lives are well known. The numbers, though, are not encouraging. The US Department of Health and Human Services has some data: 122,407 people need a lifesaving organ transplant (total waiting list of candidates). The agency said that the gap between supply and demand continues to widen.

The total number of donors from January through May this year was 5,975. On average, 22 people die each day while waiting for a transplant. Here is another statistic: Every 10 minutes someone is added to the national transplant waiting list.

"The number of people on the national waiting list continues to grow, while rates of donation and transplant stagnate."

Meanwhile, here is another story: xenotransplantation research. Advances suggest that in the future people who need organ transplants could look forward to more encouraging numbers for those placed on waiting lists.

Such activity is being carried out by a regenerative-medicine division of a biotech company. The division is Revivicor and the company is United Therapeutics.

Revivicor is after an alternative tissue source which could address the critical shortage of human-compatible donor tissues, cells and organs. Their work is producing genetically engineered pigs to provide human-compatible cells. This would be relevant for organs and tissues for use in transplant surgery, or xenografts.

Antonio Regalado, senior editor for biomedicine for *MIT Technology Review*, has a detailed look at the research, and said the team has done nothing less than "shattering records in xenotransplantation, or between-species organ transplants."

The researchers say they have kept a pig heart alive in a baboon for 945 days. They also reported the longest-ever kidney swap between these species, lasting 136 days. said Regalado.

Their approach: The pigs are "humanized" with the addition of as many as five human genes. They designed the strategy to stop organ rejection.

A Reuters report on xenotransplantation last year talked about failures in efforts to use animal organs in people in need of a transplants because of differences in the genome causing organ rejection and blood clots.

Regalado described the problem as animal organs setting off "a ferocious immune response" which even powerful drugs to block the immune attack cannot entirely stop. To beat the rejection problem, researchers started trying to genetically modify the animals.

One major step, said Regalado, came in 2003 when David Ayares, a cofounder of Revivicor, created pigs with organs lacking a sugar molecule normally lining their blood vessels. That molecule was the major culprit behind hyperacute rejection. In addition, the team made pigs with more human genes. The genetic changes make the organs more compatible with a human body.

The idea of genetically modified pigs as a link to helping to save human lives is potentially headed for static outside of biotechnology research circles. Kenrick Vezina, Genetic Literacy Project , wrote last year that " pig-grown organs would see push-back, not least of all because creating a supply of genetically modified pigs would raise all the same ethical concerns as raising the animals for meat in addition to pushing the 'unnatural' button common in opponents of biotech." Regardless, said Vezina, "pig-grown organs do seem to be coming."

According to the report in *MIT Technology Review*, Bruno Reichart, a professor at the University of Munich, called the survival of these pig hearts "a major breakthrough." He said, "It gives us all hope that cardiac xenotransplantation works." At the same time, he cautioned against assuming the transplants in humans are just around the corner. "It wouldn't be serious to give a time line for use in humans."

More information: Pig kidney graft survival in a baboon for 136 days: longest life-supporting organ graft survival to date, *Xenotransplantation*, DOI: 10.1111/xen.12174

Abstract

The longest survival of a non-human primate with a life-supporting kidney graft to date has been 90 days, although graft survival > 30 days has been unusual. A baboon received a kidney graft from an α-1,3-galactosyltransferase gene-knockout pig transgenic for two human complement-regulatory proteins and three human coagulation-regulatory proteins (although only one was expressed in the kidney). Immunosuppressive therapy was with ATG+anti-CD20mAb (induction) and anti-CD40mAb+rapamycin+corticosteroids (maintenance). Anti-TNF-α and anti-IL-6R were administered. The baboon survived 136 days with a generally stable serum creatinine (0.6 to 1.6 mg/dl) until termination. No features of a consumptive coagulopathy (e.g., thrombocytopenia, decreased fibrinogen) or of a protein-losing nephropathy were observed. There was no evidence of an elicited anti-pig antibody response. Death was from septic shock (Myroides spp). Histology of a biopsy on day 103 was normal, but by day 136, the kidney showed features of glomerular enlargement, thrombi, and mesangial expansion. The combination of (i) a graft from a specific genetically engineered pig, (ii) an effective immunosuppressive regimen, and (iii) anti-inflammatory agents prevented immune injury and a protein-losing nephropathy, and delayed coagulation dysfunction. This outcome encourages us that clinical renal xenotransplantation may become a reality.