

## MEDICAL RESEARCH

# Success for cross-species heart transplants

**A modified protocol has enabled baboons that received transplanted pig hearts to survive for more than six months. This improvement on previous efforts brings pig-to-human heart transplants a step closer.**

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Heart failure, in which the heart cannot pump blood around the body efficiently, is a problem of epic proportions. The number of adults living with heart failure in the United States is expected<sup>1</sup> to reach more than 8 million by 2030, and many of these people will die while waiting for a donor organ<sup>2,3</sup>. One possible solution to this shortage is to use hearts from pig donors instead of from humans. But, so far, monkeys given transplanted pig hearts have not survived long-term, and so this approach has been deemed too risky to test in humans. Writing in *Nature*, Längin *et al.*<sup>4</sup> report modifications to a cross-species transplantation (xenotransplantation) approach that, for the first time, has enabled baboons that received genetically modified pig hearts to survive for more than six months.

In recent years, researchers have successfully transplanted kidneys from pigs into rhesus monkeys, with the transplants functioning for 435 days<sup>5</sup>. In addition, pig hearts transplanted into baboons that still had functioning hearts have survived for 945 days<sup>6</sup>. But in the latter case, the transplanted heart was not essential to the life of the recipient. Life-supporting pig-to-baboon transplants have so far lasted only 57 days<sup>7</sup>.

Längin *et al.* set out to extend the survival of baboons receiving life-supporting heart transplants. They based their procedure on a previously described immunosuppression protocol<sup>6</sup> that prevents the baboon immune system from rejecting the pig hearts, and used pigs that had been genetically modified to reduce interspecies immune reactions. A common criticism of xenotransplantation is that the immunosuppression protocols required are too toxic for use in humans. However, the protocol used by the authors seems to have been well tolerated by the baboons, with no major immunosuppression-related infections developing. Therefore, it might also be safe for use in humans, when and if xenotransplantation has advanced far enough to allow initial clinical trials.

The authors used an optimized process for

preserving the pig hearts during transplantation. Typically, hearts are kept immersed in an ice-cold storage solution. However, the organ's tissue can be damaged when blood is recirculated through it. The researchers found that organ survival after transplantation could be improved by intermittently pumping (perfusing) a blood-based, oxygenated solution containing nutrients and hormones through the hearts at 8°C during the procedure (Fig. 1).

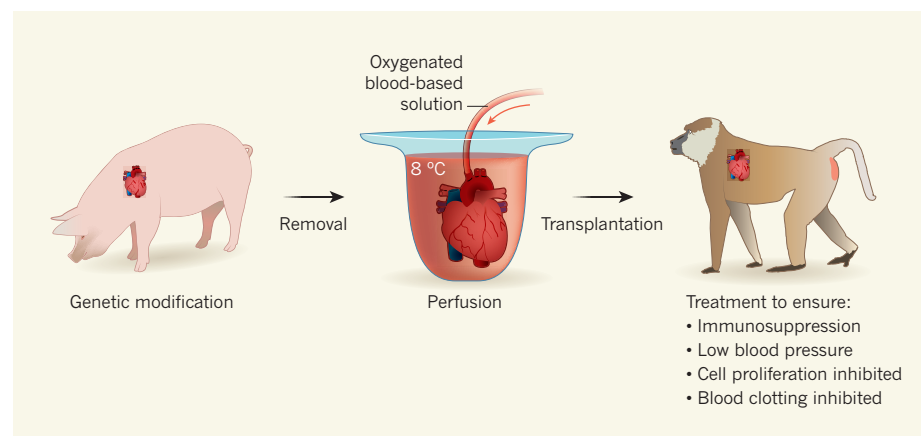
This change improved short-term survival in four recipient baboons, but the animals died within 40 days owing to rapid, detrimental growth of the transplanted hearts. Längin and colleagues therefore modified the procedure to decrease this hypertrophy, and tested the optimized protocol in five more baboons. First, they reduced the baboons' blood pressure to match that of pigs. Second, they gave the baboons temsirolimus — a drug that combats heart overgrowth by stifling cell proliferation<sup>8</sup>. Third, they modified the standard hormone-treatment regimen. The steroid cortisone is

typically given to transplant recipients to aid immunosuppression, but can cause heart overgrowth in newborn babies that receive stem-cell transplants<sup>9</sup>. The authors therefore tapered cortisone treatment much more quickly than they had for their first group of baboons, minimizing levels of the drug by three weeks after surgery.

Of the five baboons, one developed complications and was euthanized after 51 days. Two lived healthily for three months — the original designated endpoint of the experiment. The remaining two were allowed to survive for just over six months, before being euthanized.

The mechanisms underlying the consistency of transplant survival in Längin and colleagues' pig-to-baboon model need to be investigated. Nonetheless, the study's survival rate is impressive. A second finding also deserves recognition. In the past, all primates that received non-life-supporting heart xenotransplants and survived for more than three months developed a complication called consumptive coagulopathy, in which blood clotting increases in the microvessels of the transplanted heart<sup>6,10,11</sup>. This condition results from a combination of intrinsic interspecies molecular incompatibility and natural immune responses. However, Längin *et al.* showed that consumptive coagulopathy could be prevented in their baboons by combining a genetic modification used in previous protocols — one that causes pigs to produce the human protein thrombomodulin, which reduces levels of clotting — with administration of temsirolimus (which inhibits aggregation of platelets in the blood).

Norman Shumway, the great pioneer of



**Figure 1 | Improving pig-to-primate heart transplants.** Längin *et al.*<sup>4</sup> took hearts from pigs that had been genetically modified to prevent the organs from triggering immune responses in baboons, and to prevent excessive blood clotting in the heart's blood vessels. To prevent the heart from becoming damaged through lack of blood during the transplant procedure, the authors intermittently pumped an oxygenated blood-based protective solution through the hearts (a technique called perfusion) at 8°C. The baboons that received the hearts had been subjected to a previously described treatment to ensure immunosuppression<sup>6</sup>. In addition, a newly modified combination of treatments lowered blood pressure, prevented blood clotting and blocked cell proliferation, preventing detrimental overgrowth of the heart following transplantation. Four of the five baboons survived for three months or longer.

heart transplantation, is said to have believed, somewhat pessimistically, that xenotransplantation is the future of transplantation — and always will be. But the progress made by Längin and colleagues moves clinical heart xenotransplantation nearer to becoming a reality. As such, it is time to reconsider what preclinical results should be required before pig-to-human clinical trials can be initiated. Recommendations outlined by the International Society for Heart and Lung Transplantation in 2000 suggest that clinical trials might be considered once 60% of primates given life-supporting pig-heart transplants can survive for 3 months, with at least 10 animals surviving for this time frame, and with some indication that longer survival is possible<sup>12</sup>. The current study goes some way to meeting these criteria. However, it seems likely that regulatory authorities such as the US Food and Drug Administration will require a longer period of follow-up and a greater percentage of successful experiments before permitting human trials.

In addition, other issues should be given attention before pig-to-human transplants become a reality. One such issue is the potential for pig viruses such as porcine endogenous retroviruses (PERVs) to be transmitted to humans. The risk of PERV-related complications is considered to be small<sup>13</sup>, but regulatory authorities worldwide still view the possibility

with some caution. However, the genome-editing technology CRISPR–Cas has increased the speed with which pigs harbouring multiple genetic mutations can be generated, enabling researchers to produce live, healthy piglets in which PERVs have been deactivated<sup>14</sup>. This indicates one way of circumventing the risk of PERV transmission.

Another consideration is the fact that, in the past two decades, technology to improve blood circulation using mechanical support devices has evolved dramatically. These devices are used as a temporary fix while patients wait for a donor organ, but they can also be a permanent therapy for those with end-stage heart failure. The progress of this technology raises ethical questions regarding the use of pig hearts. For each patient, a case will have to be made for why a pig-heart transplant should be selected over mechanical support.

Regardless of the issues surrounding pig-to-human xenotransplantation, the blood-perfusion protocol exploited by Längin and colleagues could have a beneficial impact on human-to-human transplants. Cold static storage is still the standard for human organ transplants, but a blood-based solution could help to improve both short- and long-term results in the clinic. Moreover, it might allow the pool of donor hearts to be extended to include organs that are currently considered suboptimal because the donors are old or

have an underlying condition that reduces the heart's ability to withstand the lack of a normal blood supply. ■

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