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Commentary: One more obstacle knocked out

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The success of pig-to-baboon life-supporting cardiac xenotransplantation reported by Långin and colleagues¹ in *Nature* was a notable milestone toward turning xenotransplantation into clinical reality. However, the authors observed left ventricular hypertrophy, which led to life-limiting diastolic heart failure around 1 month post-transplant. Although the cardiac overgrowth could be controlled with antihypertensive therapy and temsirolimus, it poses a significant obstacle to clinical translation. The current study, conducted by Goerlich and colleagues,² demonstrated that cardiac xenografts from genetically engineered pigs with growth hormone receptor (GHR) knockout (KO) underwent minimal growth with preserved function for more than 6 months without adjunctive therapies.

Cardiac xenograft overgrowth was thought to be driven by both the intrinsic cause, a response to the growth hormone in recipients,³ and the extrinsic cause, an adaption to the increased afterload.⁴ One of this article's key findings showed that the intrinsic cause seemed to be the main driving force in this multifactorial mechanism. This achievement was encouraging, given that aggressive blood pressure control to overcome the physiologic mismatch may not be well tolerated in adult human recipients, and temsirolimus has not been approved for clinical use post-transplantation.

Another notable finding was that the addition of multiple genetic manipulations seems to increase the longevity of xenografts. Compared with the donor pigs used by the Munich group,¹ the GHR intact pigs in this study had additional

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CENTRAL MESSAGE

Cardiac xenografts from genetically engineered pigs with growth hormone receptor knockout developed minimal growth and maintained function for >6 months after transplantation into recipient baboons.

KO of carbohydrate antigens and knockin of human proteins in complement regulation, thromboregulation, and anti-inflammation. Although limited by the small sample sizes in both studies, these genetic modifications delayed xenograft overgrowth and functional deterioration by almost 2 months. This observation suggests a possibility of improving xenograft's immune-compatibility by adopting a combination of genetic modifications. The importance of immune-compatibility should not be overlooked, as the current aggressive immunosuppression regime with both B-cell and T-cell suppression, co-stimulation blockade, and multiple cytokine pathway inhibitors might render human recipients very susceptible to post-transplant infection.

Although the achievements deserve applause, a few questions require clarification for clinical translation. First, the underlying reasons behind the differences in the terminal physiology of the 2 groups are unexplained. Why did the GHR intact xenografts develop inflammation and space-filling defects, whereas the GHR KO ones had normal histology? Second, adult human heart to body weight ratio (range 0.45%-0.61%)⁵ is greater than that of pigs, and average adult human weight is much greater than that of baboons. The size and maturity of donor pigs for adults, and for children whose afterload is changing with time, need to be determined. Moreover, the mechanism of nonischemic continuous preservation to prevent perioperative cardiac xenograft dysfunction remains unclear. Finally, with the ventricular assist devices increasingly being used as a

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Disclosures: J.H.D. has received, through his host institution, research grant funding in the form of an unrestricted educational grant from XVIVO Perfusion, Sweden. L.W. reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Aug 1, 2021; revisions received Aug 1, 2021; accepted for publication Aug 3, 2021; available ahead of print Aug 8, 2021.

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J Thorac Cardiovasc Surg 2023;165:e82-3

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2021.08.008>

bridge-to-transplantation and destination therapy⁶ and the advent of various total artificial hearts,⁷ an ethical question of xenotransplantation over mechanical support will inevitably be raised when it comes to conduct the first clinical trial of pig-to-human xenotransplantation.

In conclusion, this study overcomes the obstacle of xenograft overgrowth by using genetically engineered pigs with KO of GHR and multiple genetic modification.

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