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Life-supporting porcine cardiac xenotransplantation: the Munich study

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Recently, Langin et al contributed an important paper to *Nature*¹, in which they reported successful pig orthotopic heart transplantation (OHT) in baboons, two of whom survived for 6 months. The authors are to be congratulated on advancing the field significantly. Their encouraging data, obtained in a challenging experimental model, support the results achieved in life-supporting pig-to-nonhuman primate kidney transplantation models, where graft survival has extended to many months or even longer than one year^{2–5}.

The Munich group appears to have overcome - at least to a significant extent - two of the hurdles that limited success of pig OHT. We would like to make what we hope are constructive comments on these two topics.

The first hurdle is achieving immediate and persistent graft function. The perfusate used to preserve the pig hearts contained thyroid hormone, and this may be a major factor in its success as there is a great deal of evidence going back many years that triiodothyronine (T3) maintains or replaces myocardial energy stores and improves cardiac function^{6,7}. The much simpler technique of cold static cardioplegia (which would prove advantageous when it becomes possible to transport pig hearts over relatively long distances) may be equally successful if T3 is administered to the recipient before and after graft reperfusion. We have observed significant reductions in plasma free T3 in baboons following either pig heterotopic heart or life-supporting kidney transplantation⁸, which we attribute in part to the systemic inflammatory response that occurs after xenotransplantation^{9,10}, and we have documented improved graft function and recipient recovery when T3 has been administered.

The second hurdle relates to the rapid growth of the pig organ after transplantation, now observed by several groups, particularly in regard to the kidney^{2,3,11,12}. The Munich group appeared to successfully prevent this by a combination of 3 approaches – (i) reduction in corticosteroid dose, (ii) therapeutic reduction in blood pressure, and (iii) administration of the mTOR inhibitor, temsirolimus. It is perhaps surprising that these measures were so successful. For example, (i) the reduced steroid dose administered to the Munich baboons is very similar to that we have administered to baboons with kidney grafts (but which grow in size rapidly for the first 2–3 months). (ii) Although reduction of the blood pressure would reduce the afterload on the pig heart, and thus might reduce the ventricular hypertrophy that

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was documented, it is difficult to explain how it would reduce the rate of growth of a transplanted kidney. Does the ventricular hypertrophy seen after OHT equate with the increase in length of the kidney seen after renal xenotransplantation, or are we looking at two separate phenomena? (iii) Sirolimus has been a standard agent administered to all of our baboons in recent years (together with an anti-CD40mAb, as in the Munich series), but does not prevent rapid growth of pig kidneys after transplantation. Again, we question whether there are different causative factors at play between pig heart and kidney transplants and, indeed, whether the two phenomena are quite distinct.

The management of the recipient baboons in Munich largely followed the Mohiuddin group's protocol, and included the continuous intravenous infusion of heparin throughout the post-transplant course. Although this might help prevent thrombosis in a heterotopic heart graft in which the left ventricle is under-filled and contracting weakly, it should not be necessary after OHT. There is little evidence that it prevents the development of thrombotic microangiopathy, and intravenous heparin has been demonstrated to be unnecessary in this respect after pig kidney transplantation.

Although there are intriguing questions to be considered and answered, the excellent study by our Munich colleagues undoubtedly represents a significant advance, and brings xenotransplantation one step closer to the clinic.

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