



## Editorial

# Xenotransplantation: Preparing the future?

## Xenotrasplante: ¿preparamos el futuro?



Julio Pascual 

Instituto de Investigación Sanitaria i+12, Hospital Universitario 12 de Octubre, Madrid, Spain

After decades of silence, organ xenotransplantation has returned to the forefront of innovation and current affairs. The ability to genetically modify litters of pigs has allowed the generation, with some success, of kidneys and hearts suitable for xenotransplantation in humans.<sup>1–5</sup> The transplantation of one of these kidneys into a recipient with no apparent possibility of receiving a conventional human kidney was a highly relevant and promising milestone,<sup>6,7</sup> despite the fact that it ultimately end up with the premature death of the patient.<sup>8</sup>

Spain is a world leader in donation and transplantation, but it does not conduct truly competitive research in the area of xenotransplantation. Spain's record for generating and implanting organs is very impressive, but not our record for innovation and research in this area. However, our leadership makes it essential for the transplant community to position itself in assessing what the exponential development of xenotransplantation may represent in obtaining organs and in overcoming the imbalance between the organs needed and those available.<sup>9</sup> It is too early to answer the question of whether xenotransplantation will one day do away with the need for organs for transplantation, or the requirement, for example, of living human donors, but there is every reason to believe that this may happen earlier than expected. There is therefore a need to begin reflecting on access and equity to this type of transplant, which could be the most disruptive advance in a decade.

Firstly, the system of universal access to healthcare in Spain suggests that there should be no inequalities in future

access to xenotransplantation for all kidney patients who need it. It is crucial to design guidelines and strategies that allow us to anticipate and avoid potential inequalities between socioeconomic groups or between autonomous communities. In Spain, there are multiple inequalities in access to kidney transplants, which have been poorly studied. The evaluation of potential recipients is still a matter based on the feelings and opinions of the nephrologists responsible for patients, and there are no agreed national criteria; nor is there any balance in the percentages or profiles of patients referred to transplant units. In some units, age remains a limiting factor, in others it is obesity, or a history of heart disease or cancer, and in others these limits are much looser and less restrictive. Contraindicating a kidney transplant on the grounds of obesity is a widespread but currently unjustifiable practice<sup>10–12</sup>: although obese people have complications, or even lower graft survival, they suffer many more complications and higher mortality while remaining on dialysis. Some nephrologists are restrictive on this issue, while others are not; some urologists exclude obese patients to avoid post-surgical complications, while others are more open in their indications. These restrictions and variability in clinical practice will be even more unjustifiable when there is no limitation on kidneys. It is essential to study these inequities and, based on an objective analysis, to seek areas of consensus and uniformity of criteria, expanding the indications and the ability of patients to access all types of transplant, including, of course, living donor renal transplants.<sup>13</sup>

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E-mail address: [julpascual@gmail.com](mailto:julpascual@gmail.com)

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All of these inequities could be accentuated when xenotransplantation becomes an available reality. Initially, it seems inevitable that this type of transplant will be highly restricted to units involved in clinical research projects associated with this disruptive practice, and there is a need to deploy strategies that allow widespread access to a theoretically inexhaustible source of organs, even before the patient needs dialysis treatment.

The debate over whether organ shortage is a good reason for restricting transplantation before dialysis will lose its relevance, given the theoretical end of this scarcity. We will no longer limit pre-dialysis kidney transplant owing to competition with dialysis patients for a scarce commodity such as human kidneys. As a result, the best option, which is preventive transplant, will become universal and access to it will need to be guaranteed conclusively nationwide. Moreover, once the theoretically inexhaustible source of xenotransplantation exists, the widespread practice of “delisting” patients with doubts about their adherence to treatment, or who are at increased risk of post-transplant graft loss, will have an exclusively economic rationale, not a shortage of kidneys, as has been the case until now. This will trigger new ethical scenarios and new challenges for nephrologists that will need to be addressed in advance.

None of this will be possible unless Spain is able to ensure that it maintains its leadership in transplantation, including in xenotransplantation, which I have defined as disruptive. Unfortunately, the key elements of the Spanish donation and transplant model that have propelled us to this position of leadership (generosity of the population, network organisation, adequate compensation for professionals) will cease to be so crucial when xenotransplantation becomes an almost routine reality. The challenge here will no longer be organisational, but rather related with innovation and financing. It is essential for both the scientific transplant community and the health administration to acknowledge something that, for the time being, merely has the status of a press release, or at most the odd scientific article: organs can now be obtained from genetically manipulated animals with relative ease.<sup>14</sup> The consequences of this acknowledgement are immediate: either strategies are developed to obtain these litters of animals and these organs in well-funded public entities, or collaboration with companies already engaged in this production matures into solid projects as soon as possible.

I would venture to say that the organisation of transplants in Spain will undergo its most profound change since the creation, 35 years ago, of the National Transplant Organisation: an industrial organ production department will overlap and, eventually, more or less progressively, replace the network for utilising potential deceased donors. Whether through the development of public programmes or by promoting alliances with private biotechnology companies, our health system will need to provide transplant teams with these organs. And here many questions are raised, such as the following: how are we going to make this difficult transition? How are we going to organise the coexistence between allotransplantation and xenotransplantation programmes? How are we going to

develop xenotransplantation programmes without adversely affecting the current programmes? Are we finally going to give patients a voice to express their opinion?<sup>15</sup> Are we going to conduct high-quality clinical trials to be sure of the efficacy and safety of xenotransplantation? Are we going to wait for countries that are more innovative in research and development to do all the work for us? And one final question/proposal: are we now going to start preparing for the future?

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