

The Ups and Downs of Xenotransplantation Research

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Because of the fear in some people's minds that the COVID pandemic will permanently halt progress in xenotransplantation research due to concerns that a pig virus will be transferred to a human recipient of an organ or cell xenograft, I have been asked to comment on what episodes caused me worry or concern during the past more than 35 years of involvement in this field of research.

Let me state immediately that, although the shutdown associated with the COVID pandemic has certainly slowed my own group's progress towards the clinic, I do not have any concerns that it will permanently prohibit clinical xenotransplantation. My reasons for believing this were published recently in a letter to the editor of *'Xenotransplantation'*, written in collaboration with Michael Knoll and Rita Bottino (Knoll 2020). Similarly, none of the previous 'scares' relating to potential infection, e.g., PERV, MERS, SARS, etc., shook my belief that xenotransplantation would go ahead as soon as we had solved the immunological problems that face us.

What has been of much more concern to me over the years has been the difficulty in obtaining sufficient funding for the expensive studies necessary for us to move forward. In the early days of xenotransplantation research, it was even more difficult than it is today to persuade the funding agencies to support xenotransplantation research. A grant application would be reviewed without major criticisms by a reviewer, but he/she would end their critique by asking, 'But is it ever going to happen?' and it would not be funded. They were correct, of course, to ask this question – it certainly will

not happen if there is no financial support. The reviewer was obviously someone with either no vision or, more likely, a quite different vision for the future.

Nevertheless, one or two research groups managed to obtain considerable financial support from major companies. For example, in the naïve belief that a pig that expressed a single human complement-regulatory protein, CD55 (DAF), combined with cyclosporine therapy, would solve all of the problems and allow us to proceed immediately to clinical trials, Novartis reputedly invested hundreds of millions of dollars into the work of the UK biotech company, Imutran. Clearly, not enough enquiry had been made into the state of the science before this investment was made, suggesting that some business executives should not have been in the high positions they held in the pharmaceutical company.

Imutran's first transgenic pig was a major step forward, and if Novartis has backed the company with perhaps \$10 million per year for a decade or more, steady progress would have been made by Imutran's excellent team of scientists, and Novartis might now be close to reaping the financial rewards of its modest investment.

When the Novartis executives realized they had been overly-optimistic, coupled with their unjustified fear of PERV, they shutdown Imutran, and killed most of the remaining transgenic pigs – in my opinion, a second foolish business decision, compounding the first.

Similarly, at Tom Starzl's urging, the University of Pittsburgh Medical Center (UPMC), the company that owns many of the hospitals in the Pittsburgh area, purchased the US pig biotech company, Revivicor, in 2004. When progress was slower

than they had been led to anticipate, they withdrew their support precipitately. Revivacor was only days away from closure when saved by United Therapeutics in 2011.

Just as with Novartis, if UPMC had been patient enough to invest longer-term, it would today be in a position to soon dominate the field of transplantation. Given the immense wealth of both Novartis and UPMC, the necessary annual investments would have been 'peanuts' to them.

Fortunately, in 2005, the US NIH's National Institute of Allergy and Infectious Diseases (NIAID) decided to support xenotransplantation research, enabling several groups to continue to make progress, which has been life-saving for the field.

I was never seduced by the lure of alternative technologies that were introduced during the past 30 years. For example, several gifted researchers were lured away from xenotransplantation by the perceived potential of stem cell technology. I was immensely skeptical that we would be able to produce a functioning kidney, heart, or liver from stem cells, at least not in my lifetime. With pigs, we already had organs that we knew would likely function well in humans. To achieve similar success from a stem cell seemed to me like the height of optimism. I had the same response to regenerative medicine, where we were promised that the decellularization of an unacceptable human organ or a pig organ, and its recellularization with cells from the potential specific recipient of the organ was going to be achievable. To me, this seemed unlikely within the next 50 years. And so, after careful consideration, and an unshakeable belief in the huge potential of xenotransplantation, it was easy for me to resist the attractions of a different field of research.

The 'lows' faced by the crises of funding were offset by the 'highs' experienced by the advances that have taken place over many years, e.g., the ever-improving techniques of genetic-engineering, the identification of the pig antigens against which humans have natural preformed antibodies, the introduction of agents that block the CD40/CD154 costimulation pathway, the identification and resolution of the dysfunctional coagulation and inflammatory responses that result from the presence of a pig graft, and, particularly, by the milestones achieved – the first islet transplant to maintain normoglycemia in a diabetic monkey for more than a year, the first pig kidney to function for more than 3 months, and then for 6 months, and even a year, the first heterotopic heart to function for a year, and the first orthotopic heart to function for 6 months. These highlights kept us believing in ultimate success.

There have been many disappointments, of course. Some of the genetic manipulations have been detrimental to the pig or have not had the anticipated effect on graft survival. At times, novel immunosuppressive regimens have proved inadequate. Some of these failures have been associated with our own lack of knowledge or forethought. Although some mistakes could possibly have been avoided by more careful planning, others were just part of a learning curve.

I once asked Norman Shumway, the major pioneer in the field of heart allotransplantation, whether he ever considered abandoning his research. He replied, "Not really. There was always just enough success - just enough gratification, if you will - that you could see that it probably would ultimately work and, if everybody kept working, we might get someplace." That is exactly how I have felt about xenotransplantation.

However, Shumway worked in the laboratory for less than a decade before he was able to move into the clinic. We have had to struggle for very much longer, and still we are not quite ready to initiate a clinical trial. Nevertheless, it has been a very interesting and exciting experience, and I remain certain we will soon get there.

“We are at our very best, and we are happiest, when we are fully engaged in work we enjoy on the journey toward the goal we’ve established for ourselves.”

Earl Nightingale.

Reference

Knoll MF, Cooper DKC, Bottino R. How the COVID-19 pandemic may impact public support for clinical xenotransplantation in the United States. *Xenotransplantation*. 2020; Jun 28:e12623.

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