XENOTRANSPLANTATION – FUTURE OR SCIENCE FICTION?

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Insight

Science fiction movies try to give us a glimpse of the future, and they often include improvements on the human body. In such films, we can see humans (or aliens) with superpowers or technical gadgets. However, this is merely science fiction - or at least far in the future - so what about other 'improvements' that we already use in the clinic: organ transplants to heal diseases or at least prolong survival. Organ failure is a severe disease that can have multiple causes and can often be treated only with organ transplantation [1]. In 2021, more than 1298 people (transplantatiestichting.nl) were waiting for a transplant in the Netherlands. Unfortunately, organs do not 'grow on trees'. Or do they?

Donor organ shortage

Donor organ shortage is a severe problem in the field of medicine [1]. Demographic trends indicate that the demand for organ transplants will continue to rise, particularly because many diseases that cause organ failure such as renal failure due to diabetes are age-related. However, as a result of improved safety, the number of traffic accidents has decreased, resulting in a decline in the most reliable source of organ donors, accident victims [2].

Xenotransplantation

People with organ failure often have only one last option: organ transplantation. Of course, organs do not literally grow on trees, but so-called xenotransplants could be an interesting opportunity in the future to resolve the problem of the worldwide shortage of organs [1]. Xenotransplantation describes the transplantation of non-human tissues. The prefix 'xeno' refers to a foreign, hence, xenotransplantation [3].

2022 – The future has arrived

In January 2022, a heart xenotransplantation from pig to human was performed at the University of Maryland in the USA. This was the first of its kind and made people feel as if they heard news which they would only expect in the far future. The surgery has been performed on a patient with end-stage cardiac failure who was not eligible for a regular transplantation with a human donor heart [4]. The patient died approximately two months after the surgery, but it can be considered a milestone that the patient survived for so long with a pig heart in his chest. So far, no details about the exact cause of death have been released.

The pig used for the procedure was a so-called 'chimeric pig' that was genetically engineered in its embryonic stage in a process called blastocyst complementation. [4]. To minimise the risk of rejection after transplantation of organs of this animal to humans, various genes were deleted from or added to the pig's DNA. Humans naturally produce antibodies against certain blood group antigens that are expressed in pigs. To avoid the immune response against those antigens, their expression was depleted in the pig. Additionally, six human genes, such as genes encoding proteins involved in regulation of coagulation and the complement system were inserted to decrease the likelihood of organ rejection. In total, the pig underwent 10 genetic manipulations [4,5].

Genetically engineered xenotransplants – an ethical solution?

Researchers and physicians are hoping that xenotransplants can help close the gap between the supply and demand of organs. However, just as the availability of human organs is associated with death, the pigs also need to die to provide the organs that can save humans. In a morbid way, those chimeric animals could be called 'living organ storages'. In a way, xenotransplantation, including genetic engineering, could potentially be superior to regular organ transplantation as it allows modification of the donor organ to provide an individually adapted treatment for the recipient [1, 5]. However, these possibilities raise an ethical question that needs to be addressed: should animals be used to 'grow what we need' in order to solve organ shortages?

Feasibility of engineered xenotransplants

In 2015, Mou *et al.* postulated that it is unlikely that blastocyst complementation will become standard practice in xenotransplantation. They raised concerns that it was unknown whether human induced pluripotent stem cells or embryonic stem cells and pig blastocysts can form interspecies hybrids [6]. However, the recent example of a pig heart transplantation has demonstrated that it is possible to grow a chimeric organ. On the other side, other concerns were addressed, including that although it would be possible to produce an organ for a specific recipient on a case-by-case basis, this would be difficult and time-consuming, and it could not meet the demands of the transplant community that requires thousands of organs and millions of cells [6]. However, are there any other possibilities besides xenotransplantation to close the gap between the requirement for and availability of transplants?

Alternatives to engineered xenotransplants

Depending on the severity of organ failure, there are indeed other opportunities that are currently being explored to provide solutions to help patients with organ failure. Cellular transplantation is considered to be a replacement for destroyed or damaged cells in organs. The procedure could, for example, involve the injection of stem cells of various types into a damaged heart, where they could potentially enhance cardiac function [7]. Using induced pluripotent stem cells, large amounts of differentiated tissues can be grown, including nerves and muscle and even possibly allow autologous

transplantation [2, 6].

For the complex organs such as livers, kidneys, and lungs, organogenesis could be a possible solution. In this procedure, organs will be grown *in vitro* or *in vivo* from for example tissue or stem cells *de novo* such as so called organoids [7]. Organoids have been recently explored as alternatives for liver transplantation and promising results showed that they can be possibly used as treatment for chronic liver disease. However, there are still challenges ahead such as clinical safety and ethical concerns [8]. Another promising alternative in the long term, in particular for cell and tissue implants, would be to graft tissues derived from embryonic stem cells [2, 6].

Sounding more like science fiction movies than reality, next-generation artificial organs are being investigated. Limitations such as reliability still need to be overcome, and, again, the complexity of the organs is a huge burden to tackle [2, 6, 9]

Currently used as a bridge to transplantation are so called total artificial hearts. Little mechanical pumps that replace the heart which are often used to bridge the time until a patient receives a donor organ [10]. Research to create such next-generation artificial hearts is underway to hopefully use them as long-term solutions, although reliable devices will take some time to develop. Complex organs such as artificial livers and lungs, remain even more distant possibilities.

Safe lives and sign up

There are various promising paths that researchers are taking in order to close the gap of organ shortage. The heart xenotransplant discussed earlier is a huge step in the right direction and should not be underestimated merely because the patient died. However, please feel free to inform yourself about the possibilities of organ donation and consider signing up as a potential donor.

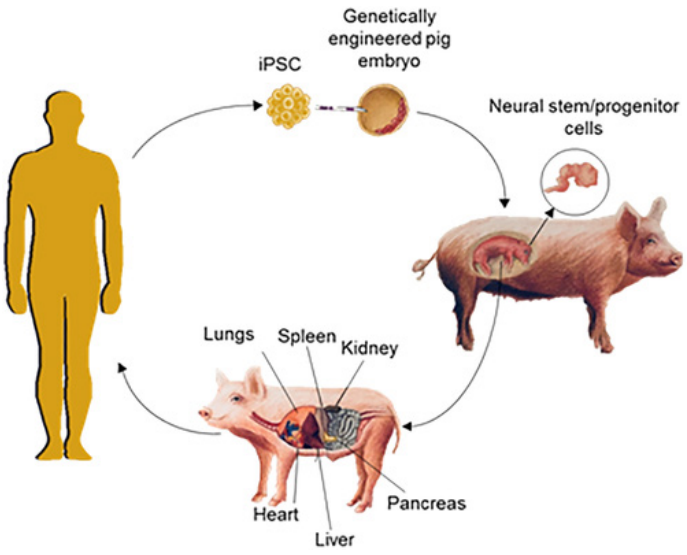

Figure 1: *Illustration of how human pluripotent stem cells are microinjected into genetically engineered porcine blastocysts before being transferred to surrogate sows. As the chimeric blastocysts develop into live-born animals, their adult organs are harvested for transplantation into patients [11].*

History tells us that procedures
that were *inconceivable* yesterday,
and are *barely achievable* today,
often become *routine* tomorrow.'
Thomas E. Starzl, 1982
(US transplant pioneer).

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