

Hiro Nakauchi: “Making organs from pigs is probably not the best solution, but right now it’s the only one have.”

01/12/2017

Hiro Nakauchi, from Stanford University School of Medicine, Institute for Stem Cell Biology and Regenerative Medicine (EEUU)

Dr. Hiro Nakauchi is one of the most important scientists in the field of Regenerative Medicine and Cell Therapy and his research explores the use of chimeric animals as receptors for the culture of human organs. Recent advances, particularly those related to the identification and generation of various types of stem cells, have broadened the repertoire and usefulness of the interspecies chimeras of mammals and have traced new paths towards the understanding of biology, as well as its possible clinical applications. In 2010, his team succeeded for the first time in the creation of rat pancreas in mouse. However, the rat pancreas generated was mouse sized and too small to perform transplantation. So his team tried a reverse experiment to generate mouse pancreas in rats. This time, the generated mouse pancreas was rat-sized and was able to supply sufficient number of islets to treat diabetic mice. In early 2017, his team reported that upon transplantation of islets isolated from the mouse pancreata generated in rats cured diabetes without immunosuppression (Nature: Interspecies organogenesis generates autologous functional islets). In addition, his group was also the first to cultivate an embryo that was part sheep, part human (human-sheep hybrid), which was the first step for the development of animal embryos with functional human organs. His studies show how the organs of one species can grow inside another's body, a method that could one day help toward the production of human tissues and organs for transplants. Dr. Hiro Nakauchi, of the Stanford University School of Medicine, [Institute for Stem Cell Biology and Regenerative Medicine](#) (USA), participated in the 2017 seminar cycle organized by the CNIC with the conference "[From Stem Cells to Organs: Exploiting the Organ Niche for Interspecies Organogenesis](#)".

- **At the beginning of this year, your group reported, for the first time the creation of a rat pancreas grown in mice that can help reverse diabetes. What is the status of that research?**

We genetically modified rat embryos so that they lacked the Pdx1 gene, a key regulator in the development of the pancreas. During the first days of embryonic life, we grafted pluripotent stem cells of mice, both induced or iPS and embryonic, into a rat embryo without Pdx1. And as a result, we obtained rats whose tissues and organs maintained cell lines of both organisms, except in the case of the pancreas that only contained mouse cells. Our final goal was to reverse diabetes and we saw that the pancreatic islets that grew in the rats were functional when transplanted into a diabetic mouse. Upon receiving the transplant, the blood glucose levels of diabetic mice were normalized long-term without immunosuppression except for the first 5 days after the procedure. These data indicates that the autologous organs generated in different species are functional and they can be transplanted without rejection. During the course of these studies, we noticed that there is a xenobarrier when we generate interspecies chimeras. We need to understand and get over this barrier to produce human organs in large animals.

- **Are animals the future in the development of organs that can be used in transplants?**

When we started this project, a decade ago, nobody, including myself, thought it would work this well. However, in the last few years we have been able to show proof-of-concept data in rodents and which we are now applying in sheep and pigs that could in the future house a human pancreas.

- **When you think about the future, do you believe there will be animal farms that produce organs to transplant in humans?**

The truth is that when you hear what you have just asked, it sounds a bit "surreal". But, on the other hand, we have to think that it is "crazy" to produce human organs on a Petri dish. Making organs utilizing a developmental environment of large animals is probably not the best solution, but right now it's the only practical one available. And, right now we think that the pigs are the most appropriate animals to cultivate human organs, although, if we see that sheep work better, there's no problem in changing that.

- **These organoids, how far are they from being used in humans?**

Far; that's why we call them organoids. They are still not completely functional.

- **You work on the generation of the kidney, lung, liver, thymus, and blood vessels. What about the heart?**

Although it seems to be a simple organ structure-wise, we still don't really know which genes intervene in its development at the embryonic stage and that complicates the process.

- **One of your lines of research is the development of platelets for their use in humans. What is the state of that research?**

We are about to complete a pre-clinical study of iPSC-derived platelets. We can generate other blood cell types in vitro, but we chose platelets because they are the most difficult blood cells to supply. Because they can only be maintained for three to four days, we constantly need freshly donated blood. We investigated pluripotent stem cells as a source of blood cells and finally, we developed a system to derive platelets from ES or iPS cells. In principle, if we have one ES cell line that is type-O and Rh-minus, we should be able to replace all the donated blood. Platelets derived from a patient-derived iPS cells are aimed at those who require repetitive transfusions due to congenital platelet deficiency. After repetitive platelet transfusion, they tend to develop antibodies which reduce the therapeutic efficacy. It is best to use platelets derived from patient's own iPSCs. Other targets are hematopoietic diseases, such as myelodysplastic syndrome. We are planning clinical trials with platelets obtained from iPS cells in Boston and Kyoto, which will hopefully start sometime next year. It is possible that in the future the donation of blood and organs will be very different from what we now know.

- **What are the main obstacles of this research?**

From an ethical point of view, we have the reluctance to the concept of endowing an animal with human genetic material. In the USA the moratorium for which federal public funds are not allocated to this type of experiment when human cells are used is still in effect. And in Japan, it is directly forbidden, although I trust that this situation will soon change. In addition, we still have to resolve the genomic distance between species, but I am optimistic in this sense and I believe that it will be overcome.

[Seminario: From Stem Cells to Organs: Exploiting the organ niche for interspecies organogenesis. Invited by Miguel Manzanares.](#)

Source

URL:<https://www.cnic.es/en/noticias/hiro-nakauchi-making-organs-pigs-probably-not-best-solution-right-now-its-only-one-have>