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The heart valve from the lab

Valves for children with a heart defect that grow with the body thanks to tissue engineering

Roughly one in every hundred children is born with a heart defect – like Jan, who came into the world almost 10 years ago with just three heart valves instead of four. Doctors implanted an animal heart valve in him as a replacement, and it worked well for a number of years. But towards the end of his time at kindergarten, Jan had to undergo another major operation. The animal donor valve was not growing with the young body, because the replacement from a pig heart is «fixed» with a chemical before use, as a result of which it is no longer a living, «dynamic» tissue. In children with congenital heart defects, such replacement valves therefore have to be repeatedly replaced with larger specimens until the body is fully grown.

Heart valves that grow with the body

It would be ideal if heart valves were available that grew into the child's heart over time after implantation. Since the beginning of the 1990s attempts have been made to achieve this goal through so-called tissue engineering. John Mayer and Joseph Vacanti made the first attempts to create heart valves in the laboratory using human cells more than 15 year ago at the Boston Massachusetts General Hospital. Simon Hoerstrup, who was also working in Boston at the end of the 1990s and is now at the Center for Regenerative Medicine, University of Zurich, has been pursuing the same objective for 12 years.

Fig.1 Prenatal Cell Sources

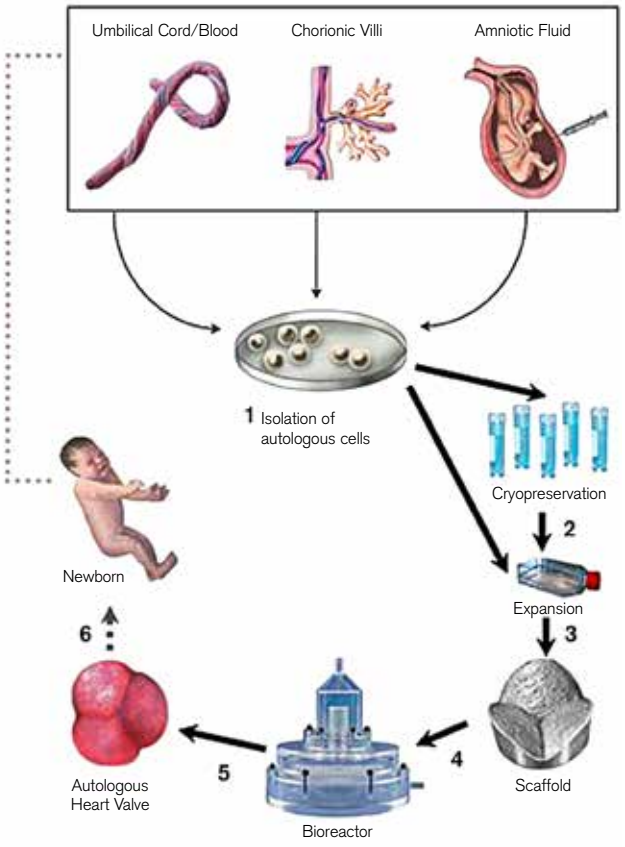

Fig.1. Concept of prenatal accessible cell sources for cardiovascular tissue engineering. (A) Prenatal cell sources for progenitor and/or stem cells e.g. umbilical cord- and/or cord blood, chorionic villi, and amniotic fluid. (B) After autologous fetal cells have been prenatally harvested (1), they can either be cryo-preserved (2) or directly further expanded (3) depending on the optimal time point for the surgical intervention. When sufficient cell numbers are reached, cells are seeded onto a biodegradable scaffold. After a short static phase, the constructs are positioned in a bioreactor (4) and conditioned. When optimal tissue formation is achieved, tissue engineered constructs (5) are available for implantation (6).

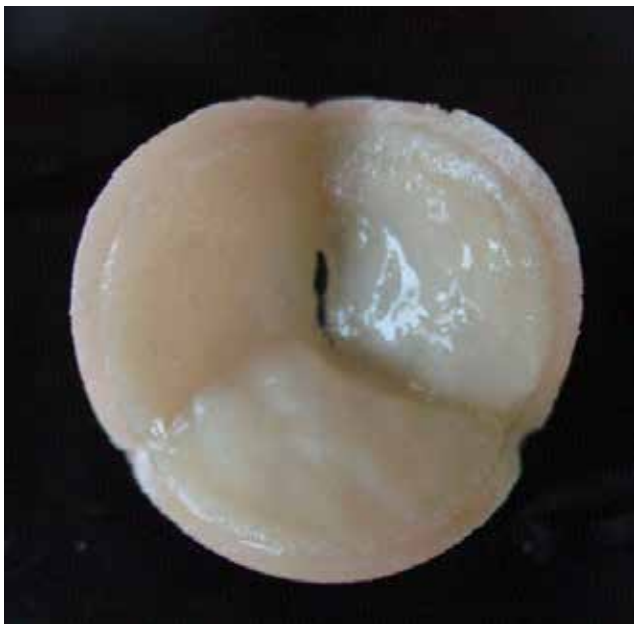

Fig. 2 Tissue engineered human heart valve based on derived-progenitor cells. Leaflets with intact and densely covered amniotic fluid-derived cells.

Heart valves must deliver optimal performance

Physicians and material scientists are cooperating here to master the challenge, since heart valves are a highly stressed body part and their structure is perfectly geared to their function. The valve material has to be flexible and at the same time stable in order to withstand the constant stresses and strains (heart valves open and shut about 100'000 times a day). The valves should be capable of regenerating, be able to grow with the child's body and be well tolerated by the immune system. For the production of this special tissue, Hoerstrup's team uses porous frameworks that are made of biodegradable plastics and are colonized in the laboratory with the patient's cells. Ideally, a tissue is produced that looks increasingly similar to a natural heart valve.

Initial success with sheep implantation

But it will probably be a few years yet before these valves can actually be used in humans. A present, the valves are still being tested in animals. Only when long-term success has been achieved could studies in humans be considered, says Hoerstrup. «In the sheep model the valves initially work well. But six months after implantation, we observe certain malfunctions that have to be remedied by changes in valve design and implantation technique.» If this eventually succeeds, there is the prospect of an interesting option stands for the treatment of children with heart defects. After preliminary animal experiments, researchers have managed to produce a suitable valve from young stem cells obtained from the amniotic fluid during pregnancy. «Using modern diagnostic methods, heart defects can often be diagnosed as early as around the 20th week of gestation,» says Hoerstrup. This would allow enough time before to make a heart valve if necessary from the child's stem cells. The first studies in the laboratory at least show that the idea is essentially feasible.

Framework made of human and animal donor valves

By contrast, another type of tissue engineering of heart valves is already in clinical use, i.e. in humans. The basic structure here does not use plastics, as in the laboratory in Zurich, but the naturally growing framework of animal or human donor valves. These are carefully freed detached the cells of the donor using chemical treatment, so that the recipient's immune system does not attack the implanted valve.

In 2008 a team from the Hannover Medical School already reported that valves colonized with cells of the recipient in the lab worked well in a study in two young people. Three and a half years after the «installation», the valve diameter was found to have increased by about four millimeters – a sign that this kind of tissue engineering can also produce valves that grow with the body.

«We have now moved away from colonizing valve scaffolds with the patient's cells in the laboratory,» says Payam Akhyari, head of the «experimental surgery» research group at the University Hospital of Düsseldorf, whose director Artur Lichtenberg was previously involved in the Hannover study. The process is said to be extremely complex and hardly feasible in routine clinical practice. Now the scaffold, whose cells have been removed, is transplanted directly into the recipient. Studies in sheep have shown that heterologous valve scaffolds, e.g. from pigs, are colonized with the «right» cells that confer the specific structure and function on the valve within a few months.

Crucial animal experiments

Animal experiments are essential here, because only they could show how the body reacts to the new tissue.«Experiments in cell culture cannot do this,» says Akhyari. Only thanks to studies in animal models was it also possible, for example, to develop suitable procedures for ensuring the cells can be reliably removed from the donor valve.

«But the sheep model has its limits,» says the Düsseldorf doctor. You cannot use it to deduce, for example, how the human immune system will react to the donor valve. In Düsseldorf they have now gone over to using the scaffold structures of human donor valves alone in tissue engineering. However, these are limited. Studies in Hannover and Curitiba (Brazil) showed that such valves work well even when implanted into the human heart, although long-term results are still pending, says Akhyari.

Rapid colonization of the valve framework

The working group led by Lichtenberg and Akhyari is now trying to establish whether pre-treatment of biological scaffolds can speed up re-colonization in the recipient's body. «We have just completed experiments in rats which show a positive effect when the valves are coated with additional substances, such as the protein fibronectin, before implantation,» says Akhyari - because rapid colonization and the formation of a full valve structure are essential: only in this way will the blood flow in the heart be optimal and the formation of dangerous blood clots on the valve surface be prevented.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mausblick aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

IMPRESSUM

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