Trachea replacement made from pig intestines

In principle, human tracheas and porcine small intestines do not have much in common. However, both have a tube-like structure. This was the basis for Dr. Thorsten Walles’ extraordinary idea. In collaboration with Professor Dr. Heike Mertsching from the Fraunhofer Institute of Interfacial Engineering and Biotechnology in Stuttgart, Walles is working on the development of methods for turning the intestines into bioartificial trachea substitutes.

Hip joints made of titanium, abdominal arteries made from polyester or cardiac valves derived from pigs – the imaginative cooperation between medical doctors and medical engineers has virtually revolutionised the treatment of many diseases. However, despite huge advances, scientists are still far from being able to replace all organs and anatomical structures with high-tech materials, animal tissue or human transplants.
Dr. med. Thorsten Walles is treading new paths in the reconstruction of tracheal defects. (Photo: Walles)
Scientists have long been searching for alternatives to replace the human trachea, a muscle tube 12 centimetres long and stabilised by cartilage rings that run from the larynx to the bronchia, but so far they have had no success.

There is huge demand for tracheas, for example to help patients suffering from tracheal tumours. Traditional methods involve the surgical removal of about 50% of the trachea and sewing the ends back together again. This has not tended to lead to serious problems. “However, if the tumour is too big, necessitating the removal of a much bigger section of trachea, then the traction is far too strong and the sutures will tear,” said Dr. Thorsten Walles, thorax surgeon at the Schillerhöhe Hospital in Stuttgart part of the Stuttgart Robert Bosch Hospital. Such patients require an implantable trachea substitute in order to survive their illness.

**Plastics prostheses do not heal well**

Attempts to replace tracheas with plastics prostheses have failed. “There have been attempts to replace damaged tracheas with silicon and other materials,” said Walles adding that the transition area between the artificial material and the tracheal tissue did not heal properly. “The trachea just does not adhere.” This, amongst other things, is due to the complicated blood supply to the trachea. The delicate vascular network surrounding the trachea is unable to supply the wound area with sufficient blood. Another problem is that the synthetic prostheses are not covered with the typical ciliated epithelium. “The lack of tracheal cilia prevents the respiratory secretions from being transported into the throat and out of the body, thus accumulating in the bronchia,” said Walles. This results in frequent bacterial infections that can be life threatening.

Now, the collaboration between Walles and Professor Heike Mertsching at the Fraunhofer Institute of Interfacial Engineering and Biotechnology (IGB) gives new hope. The researchers have developed a biological prosthesis consisting of the patients’ own cells. In a biopsy, muscle cells, connective tissue cells and endothelial precursor cells from the blood are removed and then expanded in vitro. “It is not difficult to isolate the cells,” said Walles highlighting that it is far more difficult to generate intact, functional tissue. The two researchers from Stuttgart can produce functional tissue by cultivating human cells on a biological carrier, i.e. a piece of porcine small intestine, in the laboratory. The physiological conditions of the cells are simulated in the best way possible in a bioreactor where a bioartificial trachea substitute grows. “This is tissue engineering par excellence,” said Walles.
The connective tissue of pigs and humans is almost identical

In the search for suitable carrier structures, the scientists selected intestinal tissue because the digestive organ has the same tube-like structure as tracheas. This has an enormous advantage for transplantation. Walles believes that the use of an animal intestine has no negative effects: “We deplete the pig intestine of all cells, leaving behind the three-dimensional connective tissue matrix and the blood vessels.” As the protein structure of pig and human connective tissue is almost identical, immunological rejection reactions are not expected. Nevertheless, other scientists were quite sceptical of Walles and Mertsching’s approach and instead tried to grow the human cells on a synthetic matrix. However, the synthetic approach has so far not been as successful as hoped. “Our approach is far more successful. Our biological matrix enables us to grow human tissue,” said Walles.
The first bioartificial tissue based on porcine matrices has already been transplanted into human patients. “So far, we have only transplanted small tissue patches a few square centimetres in size. We have used this tissue to close previously untreated tracheal defects,” said Walles. The first patient with a tracheal tumour was operated in Hanover, where Walles used to work before moving to Stuttgart. “The patient had spent many months on an intensive care ward. But he was able to
leave the hospital 17 days after transplantation of the bioartificial tissue segment. Follow-up examinations showed that the transplanted tissue had grown in without problems and that a layer of ciliated epithelial had already grown on the inner surface. “The excellent quality of the bioartificial tissue was a positive surprise,” said Walles. The patient lived for 16 months after transplantation when the tumour unfortunately recurred. The transplant itself had not led to any problems.

Slowly working towards clinical application

Walles has so far not transplanted a complete, long-segment tube to replace a damaged trachea, although the prerequisites for doing so have to a great extent been fulfilled. The scientists have even been able to solve the problem of sufficient blood supply. While the small-segment tissue patches are supplied with oxygen by the adjacent tissue, a complete trachea segment requires its own vascular system. This can be achieved with the same vessels that previously supplied the pig intestine with blood and oxygen. There is one more small adjustment to be made. The scientists are currently working on optimising the stability of the cartilage rings that are also produced in bioreactors.

However, Walles does not want to rush: “We want to approach the clinical application of this method slowly.” Despite all the initial successes, transplantations are still an experimental and risky intervention. There will always be setbacks. The last patient implanted with a piece of bioartificial tissue died a few weeks after surgery as a result of unexpected complications. “We are dealing with severely ill people; additional problems can be fatal,” said Walles highlighting the problems experienced. “This is why we are currently treating patients in whom established treatment methods have not led to cure or relief.” Walles and Mertsching’s team are able to give at least some of these severely ill patients new hope.

Doctors and patients interested in this new technology and its applications can download a brochure with details on the approach from the scientists’ homepages.

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