An artificial heart valve with the potential to grow

About 30,000 artificial heart valves are implanted in Germany every year. The durability of these heart valves presents a major challenge, requiring them to be exchanged time and again, especially in young patients. Researchers from the Stuttgart Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB have developed a new artificial heart valve material on which cells that are naturally present in a patient's blood can form new heart valve tissue. This tissue can grow along with the patient, and thus spare the patient repeated operations. The researchers are now undertaking preclinical studies as the first step towards obtaining regulatory approval.

Dr. Svenja Hinderer has developed an artificial heart valve that has the potential to regenerate. The young researcher is among the leading up-and-coming researchers worldwide.
© Fraunhofer IGB

Functional heart valve replacements have already become standard medical procedures. Most valves are of animal origin, but mechanical valves made of metal, to name the most frequently employed non-biological material, can also be used. Mechanical valves tend to last for the remainder of a patient's lifetime, but require the patients to be on blood-thinning medication for the rest of their lives. Biological heart valves only have a limited lifespan of around 15 years, after which they have to be replaced. Moreover, they lack growth potential and, when implanted in a child, do not grow with the child. The artificial valves have to be replaced even more frequently than in adults, and repeated surgeries are complex and stressful for young patients.

Researchers at the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart have been working for many years on the development of implants consisting of high-tech fibres that use body cells to repair injured tissue. Dr. Svenja Hinderer, who leads the Cardiovascular Systems, Biomaterials and Bioimaging working group at the IGB, and her team have now successfully developed an innovative artificial heart valve material that attracts stem cells which circulate naturally in the patient's blood and eventually replace the artificial scaffold. The scientific journal "MIT Technology Review" recently recognised the young researcher as one of the top ten "Innovators under 35" worldwide for her work on artificial heart valves.

Protein contained in biodegradable fibres attract blood cells

The idea of developing an artificial heart valve based on nature's model goes back a number of years to when the director of the IGB's Department of Cell and Tissue Engineering, Prof. Dr. Katja Schenke-Layland, was doing her PhD on heart valves and discovered that the composition of the valve matrix is key for producing functional tissue. "We wanted to continue this work, but decided to shift our focus to the extracellular matrix," said Dr. Hinderer who, after joining Prof. Schenke-Layland a few years ago, started focusing on the development of an artificial heart valve. "At the same time, a different study was being carried out on the embryonic development of heart valves and I was able to use the proteins that the study identified as important players in the development of heart valves for my own research. I produced recombinant proteins, combined them with polymers and studied the results in detail."

Svenja Hinderer found that a particular protein, or more specifically, a proteoglycan, was particularly suitable as a carrier substrate for human cells. "We were able to observe in vitro that this proteoglycan had the power to attract and bind cells," says Hinderer. "Once we had found this protein, we had to develop a method that could be used to combine the biomolecules with fibres into a material that maintains the cells in the best possible physiological environment. While a method that worked with synthetic polymers was already available, we still lacked a method suitable for proteins."

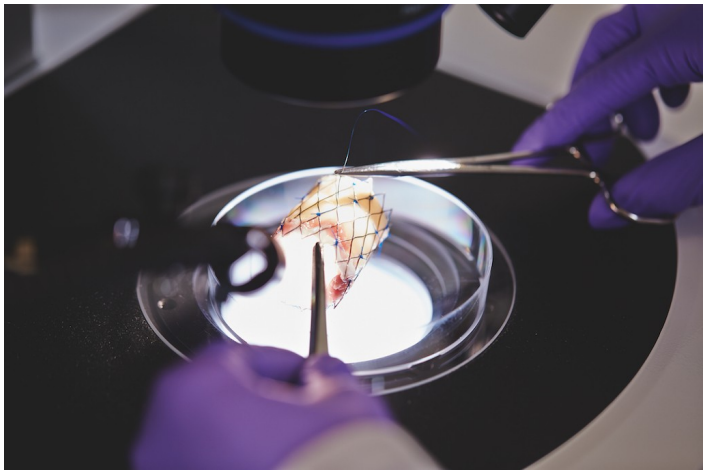
Production of robust heart valve material with electrospinning

Svenja Hinderer generated the necessary scaffolds using a method known as electrospinning which she adapted to her requirements. Nobody at the institute had experience with this method. "I built the first electrospinner that was suitable for my purposes myself. Existing electrospinners were far too big, such as those used in the textile industry," says the chemist. "At the beginning, the process was very vulnerable; for example, it was very sensitive to ambient air humidity and electrical charges, which prevented me from using the device during thunderstorms. Nowadays, excellent devices in which everything proceeds in a controlled manner are available on the market."

Besides the proteins that attract and bind cells, the artificial heart valve always has a synthetic component that provides stability.
© Fraunhofer IGB

Hinderer tested materials with a broad range of different mechanical properties, structures and architectures. "We were looking for materials that had already been approved for human application and combined them into different blends in order to capture the best possible properties," says Hinderer. The scaffolds are made of extremely thin fibres in the nanometre range. We eventually managed to produce an extraordinarily robust heart valve material that can withstand mechanical stress as effectively as the natural one. In addition, other parameters had to be fulfilled: for example, the material had to be able to absorb a lot of water. The heart valve replacement material also had to contain a synthetic component because the pressure in the aorta is so high that proteins alone cannot withstand it.

Successful reality test in the bioreactor



The artificial heart valve has already demonstrated its functional capability under laboratory conditions.
© Fraunhofer IGB

Hinderer has also developed a method for processing proteins. "It is important to hide the artificial material in a way that prevents the human body from recognising it as foreign," says the chemist. Hinderer's work was successful and she now has an artificial material that attracts and binds cells that are circulating in the blood. The artificial heart valve has yet another advantage: it is a pure, i.e. cell-free material that is only colonised by cells after it has been implanted in the body. "We decided to use cell-free material, as we were well aware of the risk that the use of a cell-based product in the human body or an approach involving stem cells would make obtaining marketing authorisation rather difficult," says Hinderer.

The artificial heart valve has already passed the reality test in a bioreactor. Hinderer comments: "It closes as well as a natural heart valve and withstands blood pressure of 120 to 80 mmHg. It also works with higher blood pressures, but results from a long-term trial are still awaited." Therefore, the scientist is now planning to carry out a preclinical study in animals in order to show that the innovative artificial heart valve remains functional in the long term. The goal is to show that, once implanted, the material attracts cells, grows with the body and is eventually replaced by the animals' cells.

Waiting for clinical studies

At the moment, the artificial heart valve is simply "a piece of fabric," as Senja Hinderer says. "But we can also spin the fibres into the shape of a heart valve. However, what the artificial heart valve that will eventually be used for human patients will look like remains to be seen. But we have wonderful results as far as the matrix is concerned. It forms reliably and looks similar to that of an 18-week-old embryo. Something that could still interfere with our plan is calcification. It is still not understood why this happens. Moreover, we are unable to simulate this process in vitro. This is why we urgently need in vivo examinations." Hinderer also mentioned that she is already in contact with suitable cooperation partners, for example heart surgeons in England and Munich.

Hinderer has already submitted an application for additional preclinical tests. This has slowed down the work on the heart valve. “In general, rather limited research funds are available in Germany and the EU, and the processing of applications takes a long time,” says the scientist. “Whilst waiting for a decision, we are trying to transfer the method to other organs, e.g. blood vessels and the heart muscle. These results are also very helpful and valuable for the further development of the heart valve.”