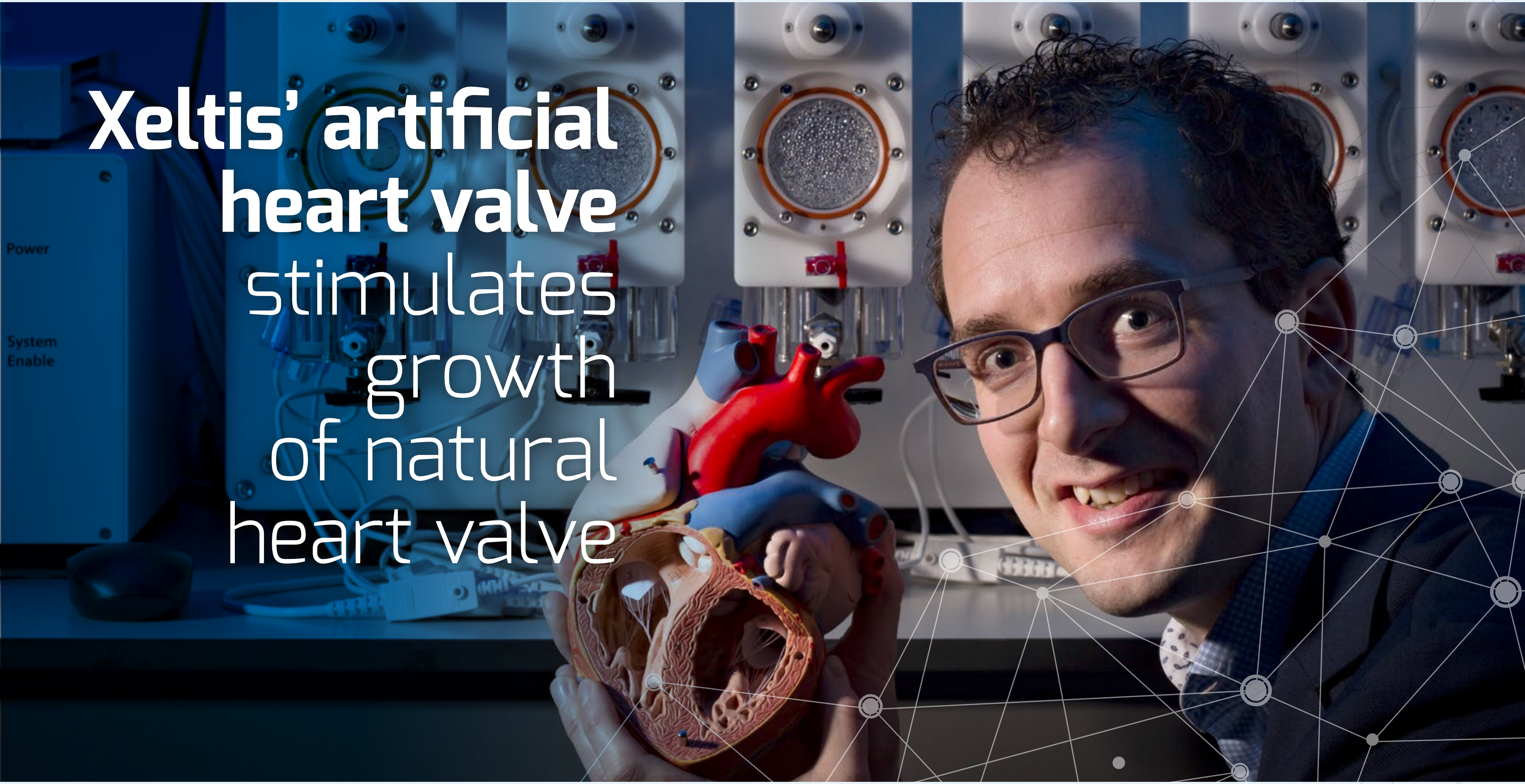
Xeltis' artificial heart valve stimulates growth of natural heart valve



"Mibiton funding enabled us to function independently straight away"

Every year, about 80,000 children are born with a failing heart valve between their heart and lungs. These children are undisposed to have an artificial valve inserted that will only last a few years, which means that during their early lives they will need three to five major heart operations. Xeltis has developed a heart valve of biodegradable synthetic material which triggers the growth of a new natural heart valve. A promising development, aided and accelerated by financial support from Mibiton.

"The concept of a heart valve that is able to regenerate itself has been known for twenty years", according to Martijn Cox, Chief Technology Officer of the Netherlands-Swiss Company Xeltis.

"The initial idea was to grow a new heart valve from the patients' own cells ex vivo by using a MAL in a bioreactor and to implant the mature heart valve into the patient afterwards. However, this is an expensive and complex method. We have developed a biodegradable heart valve that does not require the use of the bioreactor. Once implanted, the heart valve functions immediately. In addition: the porous material of the valve allows new tissue growth while decomposition of the synthetic material occurs simultaneously. Vascular cells are naturally programmed to create new cells when tissue damage occurs. Given this natural repair process, a new heart valve will form to completely replace the implanted heart valve. This simulates the process of a small cut in your finger that heals automatically without permanent scarring."

In 2006, Cox still worked as a PhD student, supervised by professors Frank Baaijens and Carlijn Bouten at the Faculty of Biomedical Technology at the Technical University in Eindhoven. Cox and his colleague Mirjam Rubbens envisaged a future for growing heart valves using natural repair processes and decided to develop this new technology in their own Company. During their graduation year in 2017 they founded QTIS/e together with the university as shareholder.

Initially they received subsidies such as a grant from the Technology Foundation STW (now NWO Applied and Technical Sciences), namely a Valorisation Grant, and a subsidy from the former Biomedical Materials programme. In 2012, *M*ibiton granted Xeltis a loan of 312,000 euro, enabling them to relocate from the University to another building on campus to establish a new laboratory.

"Without this loan, we may have been able to obtain funds, but that would have probably taken us an additional year. *M*ibiton allowed us to function independently immediately and thus we gained a year", according to Cox.

This acceleration was very helpful, because shortly after this, discussions between QTIS/e and the Swiss Xeltis (a spin-off from the University of Zurich) started which resulted in a merger. "QTIS/e and Xeltis had complementary expertise, Xeltis with raising capital and QTIS/e with R&D. Both companies fitted well together and continued under the name of Xeltis", says Cox. Because of the R&D progress made by QTIS/e, it was decided to concentrate all of the research, development, and production in Eindhoven. The number of employees in Eindhoven grew from 12 in 2012 to 35 at the end of 2016. Five people work at the head office in Zurich, mostly members of the management team. "In Eindhoven, we have created a strong development team consisting of people with complementary knowledge", said Cox. Since the merger, Cox is able to focus much more on the development of new technology as Chief Technology Officer.

The Xeltis heart valve consists of a small tube whose diameter matches that of an artery. The tube contains three small membranes that are placed at an angle to form a pointed structure. These membranes ensure that circulating blood can only flow in one direction,

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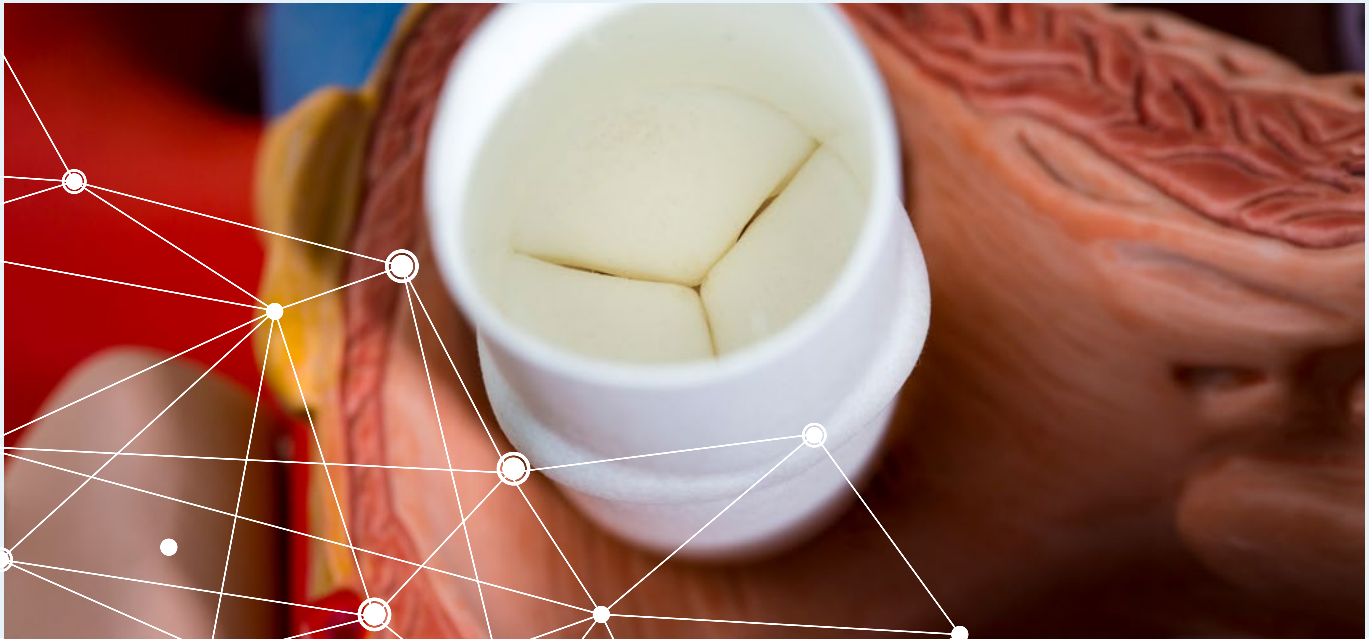
as is the case in a natural heart valve. The heart valve is made from supramolecular bonds. We mix small components that, just like DNA strands, are linked together by hydrogen bonds to create polymer chains. We are able to tune the properties of these components (building blocks) so that foreign matter in the body breaks down rapidly or slowly and is firm or less firm. This allows us to ensure that tissue growth and foreign matter breakdown is kept in a state of balance", Cox explains.

Last autumn, Xeltis entered a new development phase with their heart valve. After pre-clinical trials, the first clinical study has commenced. In the last few months a total of twelve children have had their so-called pulmonary heart valve replaced by a new Xeltis heart valve in hospitals in Kuala Lumpur (Malaysia), Bern, Budapest and Krakow. The safety of the heart valve is being researched as well as its efficacy in regenerating a new heart valve.



“We produce a passive implant, consisting of porous material, into which the cells can grow and thus allow nature to do its work”

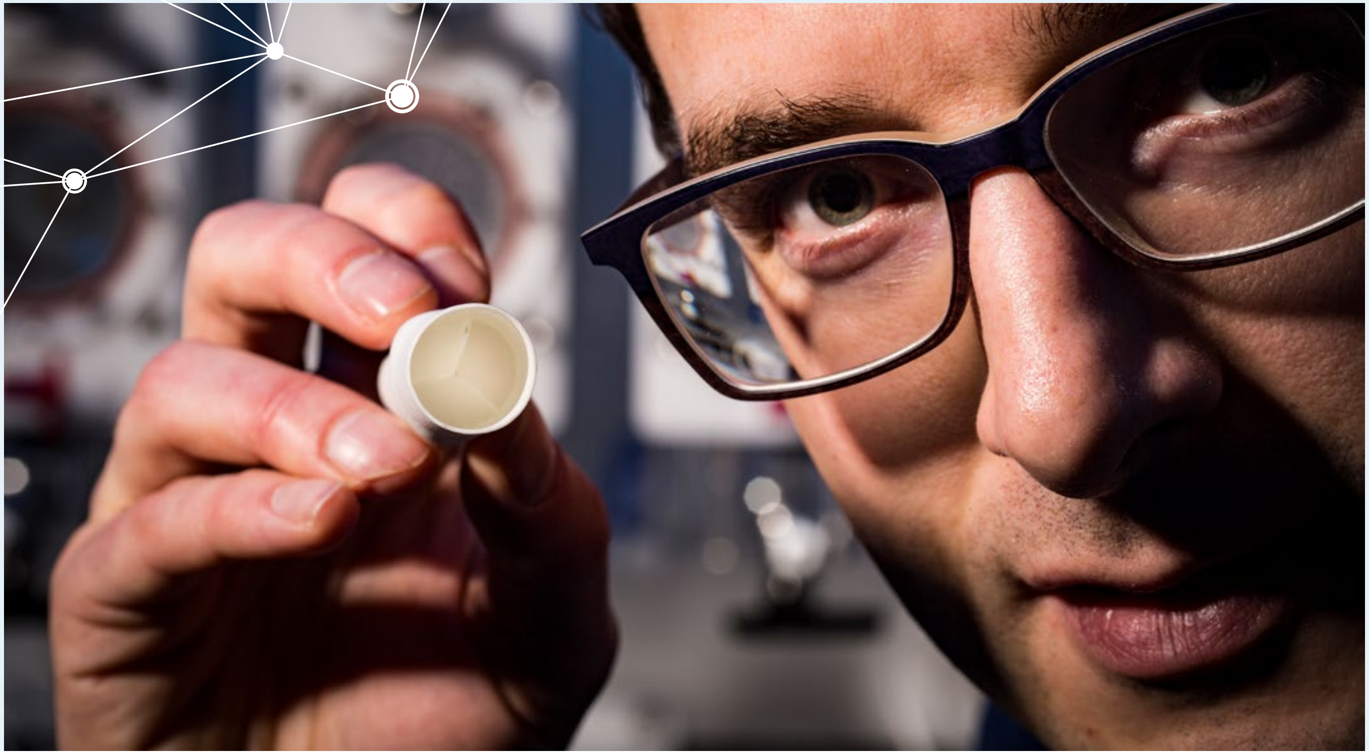
“This is a world first. In a few months’ time, we will know whether the wall of the implant in the children has been invaded by new tissue. After approximately 6 months, new tissue will also invade the small membranous valves down into the point shaped end and will thus completely replace it. The fact that the wall disappears first is no coincidence. Its structure is such that it is absorbed first. The structure of the small valve membranes will be absorbed more slowly”, according to Cox.

He emphasises that the Xeltis heart valve does not contain any drugs to stimulate or regulate natural tissue repair. There is no cell therapy involved either. “We produce a passive implant, consisting of porous material, into which the cells can grow and thus allow nature to do its work”, Cox explains.

The first clinical trial (Explore I), will be followed by a second more extensive study involving more patients. Setting up and running of the second trial will take a few more years. After this, the heart valve can be put on the market, provided that all goes well.

Xeltis has initially focused on heart valves for children with congenital heart disease, because these patients derive optimal benefit from forming a natural new heart valve. These children actually have more problems with artificial valves than adults. These regular valves are made of plastic-coated porcine or bovine tissue that cause children to develop an inflammatory response or vascular calcification and degeneration. Once the Xeltis heart valve proves to be successful in children, a similar valve for adults will be next. “Their numbers are far greater. Every year hundreds of thousands of adults in the world get a new heart valve. This is why we have already started developing a bio-absorbable heart valve for adults”, said Cox. Over time, this can also be a heart valve that can be inserted into adult patients through the groin as a compacted thin tube, into calcified arteries also. Once it is in situ, it will then uncoil using tiny metal springs. Open heart surgery will therefore no longer be required.

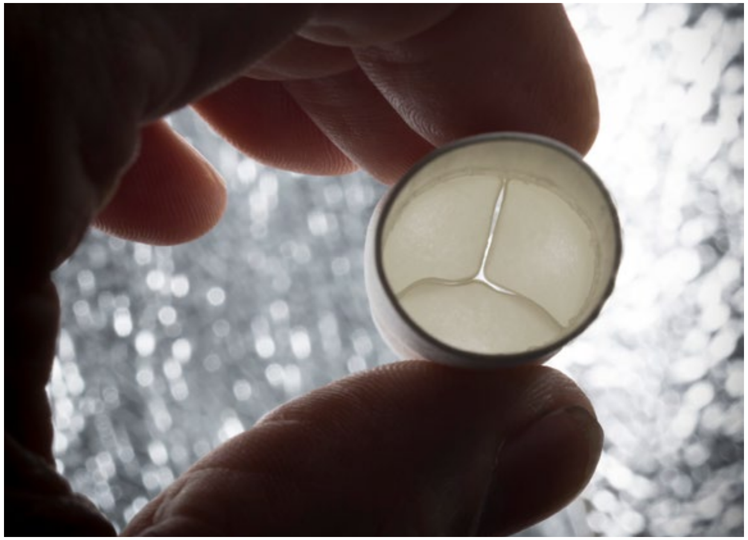
Xeltis aims to gain CE approval for the heart valve to allow the company to sell the heart valve in Europe. Xeltis already meets NEN-quality standards for cardiovascular implants (NEN-EN-ISO 13485). The expectation is that sales can start in a few years' time. Until then, there is still plenty of work to be done and the company runs on the millions in capital invested by private investors. "For the next few years we will continue to work purely on development," said Cox.



Martijn Cox, Chief Technology Officer. 'Xeltis was the first to develop a heart valve for children'

XELTIS

The supramolecular material made by Xeltis has been preceded by extensive developments. The French scientist Jean-Marie Lehn, together with the American chemists Donald Cram and Charles Pederson were at the forefront of supramolecular chemistry. In 1987 they received the Nobel Prize for this. Professor Bert Meijer of the Eindhoven University of Technology expanded on this in the 1990s and synthesised new supramolecular building blocks. In 2008 Professor Frank Baaijens and his team commenced research into tissue culture in situ (in the lab) using supramolecular polymers in a bioreactor. This was adopted by QTIS/e (later Xeltis), which now focusses on implantable bio-absorbable heart valves made from UPy-polymers (ureidopyrimidinone), which have been developed by professor Bert Meijer. Xeltis was the first to develop a heart valve for children, which also provides a frame for the growth of natural heart valve tissue. In its own cleanroom, Xeltis melts synthetic material and spins this (using electrical spinning at a voltage exceeding 1000 volts) into a thread that is wound onto a small spindle in a zigzag pattern. This is how porous material creates a heart valve.



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