The living (from the) dead

Professor Dr Carlijn V C Bouten heads a laboratory performing important research on engineering heart valves, vessels and myocardium. Alongside her collaborator Dr Dr Patricia Y W Dankers, she tells International Innovation about their biomaterial-based in situ tissue engineering experiments that ultimately seek to regenerate numerous organs.

What inspired you both to pursue a career in regenerative medicine? Why is it an interesting area of study?

From a scientific point of view, it provides an opportunity to perform research at the interface of materials science, chemistry, biology, and medicine.

One aspect we particularly enjoy is working in multidisciplinary research teams. Regeneration of the body with external stimuli and materials is challenging but, when successful, can be applied to many different tissues and organs. For this, we need an in-depth insight into the regenerative capacity of the body and discover ways to ‘seduce’ the body into repairing itself.

Contribute to the amelioration of quality of life in an ageing population and providing sustainable healthcare are key motivations too.

Could you outline the overarching aims of your research and why they are of socioeconomic importance?

Our work concentrates on achieving simple, low-cost and lifelong solutions to the complex problem of regenerating cardiovascular tissues. Instead of growing living tissues in the lab, which is the classical tissue engineering approach, we are growing tissues inside the body. By starting with a ‘dead’ synthetic material we aim to circumvent complex, expensive and logistically intricate tissue culture in the lab, as well as complex regulatory issues.

How does your approach to constructing heart tissue differ from traditional regenerative medicine techniques? What are the benefits of this novel method?

In situ tissue engineering is the key difference. Instructing cells and tissue inside the body enables us to use the body’s own capacity to regenerate. The materials we use are made of supramolecular polymers that are held together by highly directed, specific and non-covalent interactions. The interaction we employ in said materials is hydrogen bonding, in combination with additional hydrophobic and pi-pi interactions.

These supramolecular interactions give dynamics to the materials, resulting in materials that are able to adjust to either the tissue or organs they are brought into. Because of the nature of these interactions, bioactive moieties, such as peptides and drugs, can be easily incorporated (via the same supramolecular motif), through a modular approach. This results in bioactive biomaterials that are able to instruct cells and tissues.

With regard to your work on valve tissue regeneration, what are the challenges impeding its development as a clinical application? How are you addressing these issues?

The translation from bench to bedside requires intensive and prolonged collaboration between engineers, clinicians and patients. We have longstanding, fruitful collaborations in which we always aim for a result that will ultimately benefit the patient.

We have incorporated SMEs directly into our multidisciplinary research teams for acceleration and alignment of translation. Partners in our team have also developed a health technology assessment strategy to evaluate economic and clinical impact, as well as for stratification of the relevant patient groups for early-stage application.

One of the major problems is that translation is very expensive – fortunately, we are relatively successful in gaining funding for our research. Our direct collaboration with SMEs means that they can apply (and progress) the knowledge we obtain towards society in a fruitful way. In addition, we avoid the regulatory hurdles and logistical complexities associated with, for example, classical tissue engineering or stem-cell approaches for regenerative medicine. This, in turn, means that our research is attractive to investors and end-users, as it drastically reduces the clinical translation pipeline.

Finally, how do you envisage your multidisciplinary collaborations will impact society?

We are in the process of pursuing several applications; examples include blood vessel grafts (such as vascular access grafts), heart valves, and smart drug delivery to regenerate the infarcted myocardium. Ultimately, our dream is that there will one day be no need for re-implantation or any other intervention. This is of particular relevance in the case of young patients requiring an implant that needs to grow within their body.

If we can achieve these goals, the impact on society will be considerable. The realisation of these aims will be a result of our collaborations with medical doctors, engineers, materials scientists, chemists, biologists, companies and patient associations.

Contributing to the amelioration of quality of life in an ageing population and providing sustainable healthcare are key motivations too.
EACH YEAR, THOUSANDS of people receive life-saving or life-transforming transplants. Similarly, artificial prostheses help individuals perform daily activities – such as walking or eating – that often results in restoration of function and improved quality of life. The wonders of medicine and engineering have evidently contributed to society; however, the transplantation of donor organs and prosthetics is not without its problems. For instance, the reliance on donor tissues is limited by availability, and so, useful as they can be, they have intrinsic shortcomings. Likewise, artificial limbs can never truly replicate their original counterparts, and there are huge healthcare costs to consider as well.

A burgeoning global population that is living for longer necessitates the development of solutions for an increasing number of chronically ill people. Importantly, the costs of associated social welfare are also on the increase, reinforcing the need for sustainable and affordable solutions that can ease the burden placed upon society.

Considerations such as these have led to the emergence of a new discipline; namely, regenerative medicine. The body’s ability to regenerate is perhaps one of its more fascinating properties. Living cells can enable healing, for example, leading to the establishment (or re-establishment) of normal body function. Now, researchers from around the world are exploiting this regenerative property to improve lives, reduce future healthcare costs and usher in the next generation of living prostheses.

To address the pressing need for regenerative medicine solutions for priority diseases, a team of researchers at the Eindhoven University of Technology has sought to develop breakthrough technologies that ‘seduce’ the body to regenerate itself. This has culminated in situ engineered biomaterial-based tissues. This pioneering project involves multidisciplinary public-private-patient international collaborations and aims to provide lifelong solutions to cardiovascular problems.
The team has produced a synthetic scaffold that becomes a living, functional heart valve by recruiting endogenous cells to form new tissue.

**CRE@TE**

Both Bouten and Dankers helped to establish the Center for Regenerative Engineering at Eindhoven (CRE@TE), which is part of the biospired engineering track of the Institute for Complex Molecular Systems. The aim of the Center is to merge a variety of resources from a broad range of disciplines to develop in situ engineered tissues of the cardiovascular system. Rather than growing living tissues in a laboratory, they have opted to grow tissues inside the body. Beginning with a bioinspired, synthetic scaffold, implanted at the site of destination, the group has been creating living substitutes for damaged or diseased tissues. What is put into the body can be thought of as ‘dead’ but, after being implanted, this scaffold gradually develops into a living, functional part of the body. To advance this technology, a multidisciplinary public-private-patient collaboration has been established in the international consortia ‘iValve’, ‘iValve’ and the EU Seventh Framework Programme (FP7) project ‘ImaValve’.

The potential for revolutionising treatments for heart defects is there: “The benefits of synthetic scaffolds – as opposed to biological scaffolds – is that they can be manufactured on demand. We can also tailor the material’s mechanical, structural and chemical properties to yield scaffolds that mimic biological signals (bioactive), or respond to biological cues (bioreponsive),” explains Bouten. In doing this, they circumvent an expensive and logistically complex tissue culture in the lab.

**AFFECTING DEFECTS**

A young patient with a defective heart valve often needs to be operated on around two to three times throughout their lifetime, having replacements implanted that cannot adapt to body growth and are subject to wear and tear. As well as the trauma associated with repetitive surgical procedures, there is a significant cost attached to each of them. However, with the development of an in situ engineered valve originating from a synthetic scaffold, the team has made significant strides in reducing the burden placed on patients and healthcare systems.

The researchers hope that this device will ultimately be available for implantation in humans, encouraging the growth of a natural heart valve and enabling the individual to lead a normal, healthy life. The expected additional benefit will be that implanting the synthetic scaffold will only require a single operation and the valve can be implanted through the groin, meaning the surgery is minimally invasive.

**BEYOND SYNTHETIC VALVES**

Perhaps most significant is that the potential applications of this research are far-reaching and could one day provide solutions for a wide range of medical conditions. Indeed, the team is currently conducting research in nephrology, where they are hoping to ameliorate dialysis by using smart living kidney membranes based on supramolecular materials. The possibilities are vast: “Our approach can be used for almost all tissues in the body,” explains Dankers. “The challenge is to adjust the material in such a way that it has similar properties to the respective tissue.”

That their synthetic valve can be manufactured cheaply and posted to local surgeons anywhere in the world means that, once the findings have been translated for human usage, it has the potential to serve a worldwide market in a cost-effective and renewable way – something we can all take heart from.

**CENTER FOR REGENERATIVE ENGINEERING AT EINDHOVEN**

**OBJECTIVE**

To develop simple, sustainable and cost-effective solutions to regenerating cardiovascular tissues through material-based in situ tissue engineering.

**KEY COLLABORATORS**

- Professor Dr E W Meijer, Professor Dr Frank P T Baaijens, Dr Sandra Loerakker, Dr Cecilia Sahlgren, Eindhoven University of Technology, Netherlands
- Professor Dr Marianne C Verhaar, Dr Steven A J Chamuleau, Dr Eva van Roolj, University Medical Center Utrecht, Netherlands
- Dr Jolanda Kluin, Academic Medical Center Amsterdam, Netherlands
- Professor Dr A Pieter Kappetein, Professor Dr Hanneke J M Takkenberg, Erasmus Medical Center Rotterdam, Netherlands
- Professor Dr Simon P Hoerstrup, University Hospital Zurich and Swiss Center for Regenerative Medicine, Switzerland

**PARTNERS**

Dutch Heart Foundation, Netherlands • SupraPolix, Netherlands • Symo-Chem, Netherlands • Xeltis, Switzerland • Appletree CI Group, Switzerland • Medicut, Germany

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**CARLIJN V C BOUTEN** is Professor of Cell-Matrix Interaction in Cardiovascular Regeneration in the Department of Biomedical Engineering of the Eindhoven University of Technology, Netherlands. Her research concentrates on new engineering approaches to regenerate the tissues of the human heart. She leads the ‘Regenerative Medicine’ theme within the University’s strategic ‘Health’ arena.

**PATRICIA Y W DANKERS** is Associate Professor of Supramolecular Biomaterials for Translational Biomedical Science in the Institute for Complex Molecular Systems and the Department of Biomedical Engineering at the Eindhoven University of Technology. Her particular research interests are on the design and synthesis of biospired functional biomaterials.