Regenerative medicine for the heart

Professor Simon P Hoerstrup, of the University Hospital Zurich and the Competence Center of Applied Technology, on the emerging field of disease treatment by re-establishing functionality of compromised cardiovascular tissues

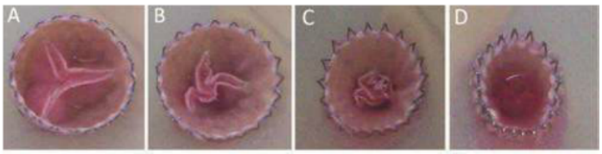
Cardiovascular disease is a major cause of morbidity and mortality, especially in the developed countries. However, successful treatment of cardiovascular disease is limited in many situations by the lack of suitable autologous tissue to restore, repair, or replace injured cardiovascular tissues. When autologous material is lacking, synthetic graft material is often used, although these materials are associated with several disadvantages, such as the significant risk of thromboembolism and calcification. Moreover, the major drawback of all current artificial replacements in paediatric application is their inability to grow. Tissue engineering and regenerative medicine are proposed as a solution to these problems by replacing tissue or organ function with constructs that are not thrombogenic, do not calcify and possess the capacity of regeneration and growth.

Regenerative Medicine Programme at the UZH

Researchers in the group of Professor Hoerstrup work on the development of such novel, cell-based therapies. Their research expertise lies in the fields of tissue engineering, cell-based therapies, and disease modelling. The main focus of cardiovascular tissue engineering is the development and *in vitro* generation of living tissues for cardiovascular surgery; including tissue engineered blood vessels, heart valves, as well as cardiac patches. Next to this fascinating field of tissue engineering, which will be explained in more detail below, the Hoerstrup group works also on the development of cell-based therapies for myocardial regeneration. They systematically assess clinically relevant stem cell sources and evaluate advanced, three dimensional stem cell delivery formats (3D microtissues) to improve myocardial functionality of the diseased heart. Based on the hanging drop method, this novel 3D microtissue technology allows for a 3D culture of different cell types that produce endogenous extracellular matrix environments with improved adhesion properties. Another aim of the group is to better understand the cellular and molecular mechanisms in cardiovascular disease. By disease modelling they study, for example, the inflammatory processes that occur in the early development of arteriosclerosis.

Cardiovascular tissue engineering

Tissue engineering of blood vessels and heart valves enables the *in vitro* production of autologous, living and functional replacements with the capacity of regeneration and growth. The latter is of particular importance for paediatric application as an alternative to state-of-the-art artificial replacements. In recent years, research



'Crimping' of a tissue engineered heart valve prior to trans-apical implantation (Schmidt, Driessen, Dijkman, et al., *JACC 2010)*

has demonstrated the principle feasibility of the autologous tissue engineering concept for cardiovascular applications in heart valves and blood vessels in preclinical animal studies. The success of these tissue engineered cardiac constructs dependents on three main factors: the proliferation and differentiation potential of the cell source from which a living neo-tissue is grown; the scaffold matrix, which determines the three dimensional shape and serves as an initial guiding structure for cell attachment and tissue development; and the *in vitro* culture conditions of the living construct before implantation. This *in vitro* 'conditioning' can be influenced by the culture media and mechanical stimulation such as pulsatile flow by using bioreactors.

Tissue-engineered large diameter vascular grafts have been successfully used in low and systemic pressure applications in sheep, and technology transfer to human cells has been shown. In a large animal study, Hoerstrup *et al.* (*Circulation* 2006) investigated the function and growth in tissue engineered living main pulmonary arteries over a period of 100 weeks in a lamb model, covering the full growth of this animal model. With this investigation the Hoerstrup group demonstrated first evidence of the functional growth in living pulmonary arteries engineered in the laboratory.

Additionally, the group demonstrated that these living tissue engineered blood vessels were functional in preclinical large animal trials up to four years (*Circulation* 2006). These findings support the potential of the tissue engineering concept for congenital applications. Important observations were: the *in vivo* remodelling of the tissue engineered arteries into the typical three-layered architecture observed in their native counterparts; and the ability of the tissue engineered arteries to follow the normal anatomical growth of the animal and their remodelling to a stable, mature tissue composition.

Based on these results, the University of Zurich received permission from the European Regulatory Authorities for a first-in-

Collaborative (inter-) national projects

The Hoerstrup group participates in several collaborative (inter-) national projects. For example, the SNF-SPUM consortium with the main objective to develop an efficient cell therapy concept for the cardiac repair. This collaborative project, led by Professor Hoerstrup, is financed by the Swiss National Foundation and brings together three academic partners in Switzerland. Additionally, the group takes the lead in the EU FP7 LifeValve consortium, which is a large collaborative project funded by the European Commission that brings together a unique consortium of academic and industrial partners from Switzerland, Germany, the Netherlands, Austria and Hungary. The objective of the LifeValve project is to develop a new therapeutic strategy to treat heart valve disease more efficiently, by developing a clinically relevant tissue engineered heart valve that enables regeneration and growth and can be implanted by minimally invasive catheter technology. This highly interdisciplinary approach combines basic sciences, medical research, engineering and clinical practice. Recently, group member Dr Petra Dijkman was awarded with an EU FP7 Marie Curie Intra-European Fellowship for Career Development (IEF). In this fellowship she will focus on the improvement of the clinical applicability of the tissue engineered vascular grafts, as new regenerative therapy for children with congenital cardiovascular malformations.

man (FIM) clinical pilot trial using tissue engineered vascular grafts for patients with congenital heart malformations (single ventricle pathology). This FIM study will be realised in close collaboration with the Swiss Center of Regenerative Medicine (above right) and may provide a further basis to justify the large scale clinical implementation in the near future. Meanwhile, the recently awarded Marie Curie Intra-European Fellowship (above left) will fund the research to improve the clinical applicability of these tissue engineered vascular grafts as new regenerative therapy for children with congenital cardiovascular malformations.

Heart valve tissue engineering represents another promising scientific concept to overcome the limitations of current artificial non-living replacements. More specific, current options of surgical heart valve replacement are either the mechanical valves, which require lifelong anticoagulation therapy, or fixed biological xeno- or homografts that suffer from structural dysfunction due to progressive tissue deterioration, causing limited durability. As heart valve disease is a significant cause of morbidity and mortality worldwide and the number of patients requiring heart valve replacements is approximately 280,000 annually worldwide, the clinical need for good replacements and implantation techniques is high. Although, new minimally invasive implantation techniques have recently emerged as a good alternative to conventional surgery, their application is currently limited to elderly high-risk patients due to bioprosthetic prostheses, which are inherently associated with progressive dysfunctional degeneration.

To enable the broader use of these promising less invasive techniques in younger patient populations as well, the Hoerstrup group investigated the feasibility to merge transcatheter-based technologies with heart valve tissue engineering (Schmidt, Driessen, Dijkman, *et al. JACC* 2010). Following the successful merging, they recently introduced the concept of decellularised homologous tissue engineered heart valves to substantially simplify the current heart valve tissue engineering approaches towards routine clinical translation. By decellularisation of the engineered valves, they eliminate the complex methodologies of the classical tissue engineering concept, such as cell harvest, cell expansion, seeding on scaffolds, *in vitro* bioreactor culture, and resulting high logistical and financial efforts. The engineered off-the-shelf accelular valve replacements that showed large recellularisation capacity have potential as a promising alternative to the current artificial non-living replacements (Driessen, Emmert, Dijkman, *et al. JACC* 2012). Moreover, in the large collaborative EU FP7 project LifeValve (above left), it is aimed to merge these promising valve replacements with trans-catheter implantation techniques.

GMP Cleanroom facilities at the Swiss Center for Regenerative Medicine

The first Swiss Center for Regenerative Medicine (SCRM) is part of the Competence Center for Applied Biology and Molecular Medicine (CABMM) and is focused on the clinical application of regenerative medicine and cell-based therapies. The interdisciplinary translational research centre is the core facility to conduct tissue engineering and guarantee safe storage for engineered constructs under Good Manufacturing Practice (GMP) conditions. The SCRM aspires to be the premier Swiss focus for research, training and technology transfer in regenerative medicine and facilitates the existing and increasing demand for the clinical application of newly developed cell-based therapies. The SCRM aims to process patient cells for tissue engineering and cell-based therapies that can be used for clinical trials or stored in the cell and tissue biobank. The SCRM provides GMP clean room technology to academic partners and industry. With the unique location at the Zurich University Hospital they offer direct links to research units, clinics, labs and the Center for Clinical Research.

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