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It is not every day you get to build a heart

Heart, and other solid organ (e.g. kidney, liver), transplantation has become the gold standard for end stage organ failure. Transplantations substantially outperform any other available treatment and extend life by an average of 15 years in the case of heart transplantation. However, two major problems remain, a dire shortage of donor organs and organ rejection requiring immunosuppression.

Organ rejection is a complex reaction to donor tissue mainly initiated by recognition of foreign (donor) cells and specific antigens on the cell surfaces.

Immunosuppressive drugs are used to suppress the recipient's body from rejecting the transplanted organ. Lifelong immunosuppression is required by the patient who always remains at some risk of rejecting the organ. Immunosuppression results in a higher risk of infection and is associated with the development of hypertension, kidney failure, accelerated atherosclerosis and coronary artery disease and immunosuppressed patients are at risk of developing certain cancers, like lymphoma.

It was, therefore, logical that attempts were made to decellularize solid organs, removing all living cells and their remnants from the donor organ, in order to produce a biological scaffold consisting only of its connective tissue. The premise is that the solid organ scaffold can be reseeded in the laboratory, using cells from the transplant recipient's own body, and at a certain stage of development, be implanted in the recipient. This bioengineered organ will then not require immunosuppression and is literally tailor made for the recipient.

Researchers at the University of the Free State, lead by Profs Francis Smit and Pascal Dohmen (extra ordinary professor at the UFS from the Charite University in Berlin), have announced that, using animal heart models, they have successfully completed two essential experimental phases in this process. Firstly, a decellularized whole heart scaffold has been produced in a baboon model, and secondly, they have successfully cultured beating rat heart cells in the laboratory.

The pioneering work of Drs Doris Taylor and Harald Ott at Minnesota and Harvard Universites is recognized. Dr Taylor successfully produced the first beating rat heart in the laboratory.

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American and European researchers have used the process of decellularization to produce rat and pig heart scaffolds, but the research team at the UFS has produced primate heart scaffolds using a decellularization process developed in the department. This is an important research step, as the baboon is the animal that is genetically the closest to human beings.

We use a modified heart lung machine circulation system in the whole heart decellularization process. The process involves washing and cleaning the hearts and then connecting them to the machine, which circulates detergents and enzymes that cause cell death and destruction, with minimal damage to the connective tissue of the heart. After washing and irrigation with normal salt concentration solutions, the hearts are studied. Prof Smit explains that it is much more difficult to decellularize large animal organs than, for example, rat hearts. Thus far, the researchers have been able to eliminate more than 90 percent of cells and are modifying the decellularization process. The results are in line with other groups working on larger organs.

In order to recellularize the heart scaffolds, specific cell lines from the recipient will have to be cultured. These include endothelial cells, lining the vessels, fibroblasts, involved in maintaining sub structures of the heart and importantly, contracting myocytes. These cell lines can then be introduced to the heart scaffold, using a bioreactor. The researchers have successfully cultured endothelial cells and fibroblasts in the rat model and using neonatal rat hearts, have managed to culture living, beating heart cells in the laboratory. The selective use of induced pluri-potential cells is envisaged in future. Reseeding the heart with the right number of cells, getting the cell ‘mixture’ right, endothelialization of the vasculature and judging what ‘enough’ is before implantation remain important challenges.

The final step would be to connect the bioengineered heart to the recipient. The implantation can be performed as a fully developed transplanted heart expected to maintain the circulation from the start or rather, in the researchers’ view, using serial modifications of the heterotopic or ‘piggy back’ transplantation operation described by Prof Chris Barnard as a partially developed heart, maturing within the recipient.

Using these connections, it is possible to use the heart as a support or assist device of the right ventricle, the left ventricle or the whole heart.

Although years of research lie ahead before this becomes a reality, the University of the Free State has become a serious international participant in this exciting field of research and development. In recognition, Prof Smit has been invited to present his work on tissue scaffolds at the Bioengineering Forum at the European Association of Cardiothoracic Surgeons (EACTS) Annual Conference in Milan in October 2014.

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Prof Smit and his team started focusing on decellularization in order to develop pericardial patch tissue and decellularized homografts (heart valves harvested from cadavers) for use in cardiac surgery and as valve replacements in an African setting where these replacements are required in a relatively young population due to rheumatic heart disease. In young people, biological or tissue valves as well as homograft and other tissue conduits deteriorate, calcify and fail as a result of continuing immune responses after implantation. Decellularizing tissue has been shown to attenuate these responses especially in young patients and children.

A decellularization and sterilization process has been developed at the UFS and is presently being patented. The UFS also runs the only homograft bank in South Africa and has been active since 1986; having processed over 2 000 valves for implantation in South African and international cardiac surgery centers.

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