Introduction. Bioengineering the heart

The heart of creatures is the foundation of life, the Prince of all, the Sun of their micro-cosmos from where all vigour and strength does flow.

William Harvey (1628): de Mortis Cordis.

Cardiovascular disease continues to be one of the major causes of death and suffering both in the developed and developing countries (Kannel 2000; Stewart et al. 2002, 2006; Young 2004; Silwa et al. 2005). It is estimated that 9.5 million individuals died of cardiovascular disease in 2005. This highlights the urgent need for developing effective means of preventing and treating heart disease. Such efforts should be developed seamlessly and must benefit from each other. Damage to the essential components of the heart such as heart muscle or valves can result in irreparable damage, which can only be treated by replacement using either mechanical (Copeland et al. 2004; Puvimanasinghe 2004) or biological substitutes.

Although there has been considerable progress in developing and using mechanical devices, they cannot match the elegant sophisticated functions of living tissues. The twentieth century has witnessed the successful application of tissue transplantation, which included heart and valve tissues (Ross 1967; Morris & Tilney 1989). However, these procedures are markedly limited by the scarcity of donor organs (Hertz et al. 2006) and the current lack of strategies for inducing specific immune tolerance. The alternative of engineering tissues and organs (Nugent & Edelman 2003; Lavik & Langer 2004) such as the heart and heart valves is a rapidly growing branch of science and medicine stimulated by massive need, commercial interest and scientific curiosity. Achieving such ambitious goals, however, requires coordinated efforts of clinicians, biologists, engineers, chemists and physicists coupled with imaginative thinking on the relationship between form and function.

In this issue of Philosophical Transactions, we attempted to bring together several experts representing each field to review this exciting topic as it applies to the heart. We have encouraged the authors to expand, if they wish, into their areas of expertise, which we believe adds more clarity and enriches the topic at the expense of minimal overlap and/or divergence.

In attempting to recreate an intricate organ such as the heart, it is of utmost value to understand how it was formed in the first place. Current knowledge in the very rapidly advancing field of developmental biology of the heart is presented by Moorman et al. (2007). Successful tissue engineering (TE) depends on accurate characterization of the structure, function and regulation of each component of the tissue to be engineered at molecular, cellular and tissue levels, coupled, whenever possible, with describing strategies for reproducing some or all of these characteristics. Parker & Ingber (2007) discuss the structural and functional integration, in both time and space, of a wide range of structures and processes within the myocardium, which are tightly regulated and which work in harmony. They emphasize the important role of mechanotransduction from the extracellular matrix (ECM) to the intracellular cytoskeletal system in regulating such fundamental processes as gene expression, myofibrillogenesis and electro-mechanical coupling. Using this knowledge, they describe novel approaches to myocardial tissue engineering using two-dimensional microfabrication techniques which should pave the way to replicating some aspects of native heart function.

One of the important components of the ECM is collagen with all its types. Apart from their important function in maintaining structural integrity of the tissue and in force transmission, collagens have been shown to influence cellular function through two-way communication systems. The article by Koid (2007) details some of these functions and relates them to the structure of the collagen molecule. In addition, he describes exciting approaches to the production of designed synthetic triple-helical peptides that could reproduce these functions and could be extremely valuable in TE. Similar approaches to the production of synthetic substitutes for fibronectin and possibly other ECM components are being tried (Sagnella et al. 2005). The structure and functions of elastin, coupled with their regulation, are discussed by Kiely et al. (2007) while the use of biological matrices and bionanotechnology is presented by Taylor (2007).

TE involves the use of a variety of many types of cells that change their form and function both during and after insertion in the body. Monitoring cell function during manufacture and later using biosensors represents another form of extremely promising technology which is reviewed by Cass & Toumazou (2007).

Advances in cardiac magnetic resonance have allowed in vivo study of the complex fibre orientation in the myocardium and the elegant flow characteristics through the heart, coupled with regional and global characterization of human myocardial perfusion, function and structure. This important topic is described by Yang et al. (2007).

One of the main issues in TE is to produce off-the-shelf living tissue products. This requires the use of non-self tissues which will raise the problem of rejection and necessitate strategies for inducing tolerance, preferably in the engineered tissue cells or organs. This topic is reviewed by Batten et al. (2007).

Attempts at producing three-dimensional cardiac tissue constructs that could be used to replace or enhance parts of the heart are being developed using...
several strategies. Gordana Vunjak-Novakovic and colleagues (Radisic et al. 2007) describe in detail the use of a series of processes emulating normal (biomimetic) to achieve this goal with extremely interesting early results.

The second part of this issue of the journal is devoted to TE heart valves. Heart valve disease is increasing worldwide with an estimated number of 80,000 individuals requiring valve replacement by the year 2020 (Yacoub & Takkenberg 2005). Up until recently, heart valves were thought of as passive structures that follow the movement of blood. Recent evidence has shown that heart valves perform a number of extremely sophisticated functions which depend on their continued viability (Yacoub et al. 1999). These functions are thought to be important for enhancing both the survival and quality of life after valve replacement (Yacoub & Cohn 2004a,b). The engineering aspects of these functions and their biological correlates are reviewed by Sacks & Yoganathan (2007). While many of these functions can be studied in vivo and in vitro, the development of mathematical modelling represents an important additional means for investigating valve function. Kunzelman et al. (2007) reviews this topic particularly in relation to mitral valve function in health and disease. Some of the intricacies of aortic root function, as viewed by a surgical group, are presented by Allen Cheng and Craig Miller (Cheng et al. 2007). As emphasized repeatedly in this issue, valve function is closely dependent on structure. Details of the micro- and macrostrucure of heart valves are reviewed by Hans Sievers (Misfeld & Sievers 2007). The specific function of valves is executed by several cells of very particular nature. Essential features of the valve cells, particularly those populating the interstitial compartment, are reviewed by Chester & Taylor (2007), while different aspects of the newly discovered features of valve endothelial cells and their response to shear stress, including the signalling pathways responsible for these responses, are reviewed by Butcher & Nerem (2007) and Frangos (White & Frangos 2007). Apoptosis plays a major role in endothelial cell function both during different developmental stages and later in life. Studying the regulation of this essential function using novel methods is reviewed by Chris Print and colleagues (Affara et al. 2007). Understanding the process of valvulogenesis during embryonic life, including the origin of cells and molecular and physical interaction between cells and ECM, adds a new dimension to the topic of TE heart valves. This important topic is reviewed by Butcher & Markwald (2007) whose laboratory has been responsible for many of the advances in the field. Strategies for TE heart valves is then presented by Dörthe Schmidt and Simon Hoerstrup (Schmidt et al. 2007).

The issue ends with an article on the interrelation between form and function as seen by a sculptor (Gormley 2007). This exemplifies the close relationship between art and science. It is hoped that the information presented in the issue will accelerate progress in the field that has scientific value, and most importantly have a potentially large impact on global health.

**REFERENCES**


