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Bioengineering of Transplantable Organs

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Editorial

One of the most promising directions in transplantation (Tr) today is tissue and organ bioengineering. The term tissue engineering is defined as manufacturing body parts *ex vivo*, by seeding cells on or into a supporting scaffold. Tissue engineering and regenerative medicine (TE/RM) share the same ultimate goal as organ transplant: the creation of functional tissues or whole organs and their use as 'replacement parts' for the human body. The main advantage of this technology is the use of autologous cells that eliminates the need for immuno suppression (IS). Successful achievement of this goal may play a groundbreaking role in clinical Tr.

Bioengineered organs represent a new, theoretically inexhaustible supply of organs that could satisfy the growing demand for organs and reduce waiting list mortality. Furthermore, if generated from patient-derived cells, bioengineered organs could also be transplanted without need for life-long IS, eliminating its side effects and costs. In addition, regenerative medicine technology could be used to improve the quality of discarded donor grafts.

The first successful tissue engineered urinary bladder was transplanted in 1999 in the patients with myelomeningocele. At 46 months of follow-up, the new bladders showed improved function, compliance, and capacity [1]. Five years later, the same group has performed the first successful bioengineered urethral transplant in five boys with congenital urethral malformations [2]. Shinoka et al. [3] reported the first bioengineered blood vessel implantation in a child who was suffering from single right ventricle and pulmonary atresia. This was followed-up by the first implantation of fully autologous vessel grafts in nine hemodialysis patients [4].

However, bioengineering of a whole functioning organ is an extremely complicated task. Significant advance on that way came in 2008 with the discovery of decellularization techniques that led to the development of a whole organ scaffold with intact three-dimensional geometry and vasculature. The big step forward in this direction was *ex vivo* production of a functioning heart in 2008 [5]. After complete decellularization of rat hearts it was repopulated by intramural injection of neonatal cardiac cells and perfusion of rat aortic embryonic cells (EC). After maturation, the recellularized structure resumed macroscopic contractile function and was able to generate pump function. For the first time, whole organ was manufactured *ex vivo*. This approach has been applied successfully to engineer small livers and lungs from rodents. The first transplant of a human bioengineered organ was reported by Macchiarini et al. [6]. The authors transplanted bioengineered windpipe using patient's own stem cells [6].

The whole kidney scaffolds have been derived through decellularization of rat, pig, and rhesus monkey kidneys. Renal extracellular matrices produced from porcine kidneys have been implanted into pigs *in vivo* as a proof-of-concept. Furthermore, Song et al. [7] reported the regeneration of functional rat kidneys that were seeded with epithelial and endothelial cells and produced some urine when transplanted in rats. Future directions for kidney bioengineering are renal progenitor cell isolation, differentiation, expansion, and optimization of cell seeding protocols and culture.

This novel approach opens the door to completely new and very promising perspective. The use of animal-derived scaffolds rather than human ones can validate the concept of "semi-xenoTr" [8]. While in xenotransplantation the whole organ is animal-derived, in semi-xenoTr only the scaffold is animal-derived. Theoretically, this approach could overcome hyper acute rejection and the risk for transmission of zoonoses that to date have restricted widespread application of xeno-Tr. Indeed, pilot experimental studies in porcine to ship transplants have ruled out the transmission endogenous retrovirus genome.

Although we are still a long way from understanding how stem cells may generate viable complex organs, it is reasonable to predict that stem cells may revolutionize regenerative medicine and organ Tr in the future. On the background of current achievement briefly described above, the

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main challenge today is the bioengineering of complex parenchymal organs (kidney, liver etc.) for human Tr. As recent reports have shown, decellularization/recellularization techniques can be applied to human organs such as kidney, lungs, and small intestine. However, a major challenge still exists in the complete repopulation of these whole organ scaffolds, which is necessary to produce a clinically functional organ. Identification of a cell source that has the potential to proliferate after scaffold seeding may offer a solution. Lastly, the use of discarded human organs, with a complete patient history, can facilitate regulatory approval of these scaffolds for clinical use.

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