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Dream or reality?

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Organ replacement therapy has become one of the main medical activities in elderly patients in the Western world. Estimations raise numbers of 50 Mio patients who have sustained or are supported by an artificial organ or a transplant worldwide. The economic burden is enormous and represents about 10% of the total healthcare spending.

Vascular replacement therapy is required in growing numbers as for example half a million coronary bypass grafting in the US alone. In the case of lacking autologous graft material, synthetic, seldom biologic (homo/xenografts) prostheses are required. However, the long-term clinical results of small caliber vascular prostheses (internal diameter smaller than 6 mm) is very poor. Therefore, major efforts to find new alternatives or create better scaffolds for vascular tissue engineering, have been undertaken in the last decades. From the originally introduced synthetic, non-degradable prostheses (Dacron®) by de Bakey over 50 years ago, industry has now moved to other materials, such as expanded-polytetrafluoroethylene (ePTFE). The results are still sub-optimal and therefore such prostheses are not used for coronary bypass grafting. During the last two decades, concepts of tissue engineering, as pioneered by Langer and Vacanti, have spread in the academic world, but so far such prostheses have rarely reached clinical application and none have been manufactured industrially.

For a successful tissue-engineered vascular graft, a great number of requirements are needed such as good surgical handling, biocompatibility, thrombosis and infection resistance, appropriate healing and mechanical properties, including an artery-like compliance. Additionally, easy manufacturing, sterilization and shelf-readiness would be helpful. The ingredients for building a new vessel consist of:

- a three-dimensional matrix or scaffold which can be stable, degradable, synthetic or natural
- mediators, growth factors and drugs which would optimally be released locally
- cells which can be added before implantation and matured in a bioreactor (in vitro approach), or which can grow into the scaffold by using the right ultra-structure or cell triggers (in vivo approach).

Advantages of in vitro cell seeding consist of the possibilities of using different autologous patient-derived or stem cells which are aimed at reconstituting the three basic layers of a vessel. The disadvantages of this method are the time, manpower and cost required to mature such a vascular graft in a bio-reactor. This approach has been shown to be scientifically successful. However, so far neither large-scale applications nor shelf-readiness are available.

First steps in the way of cell seeding were started by the groups of Ann Arbor, USA and Vienna, Austria, performing autologous endothelial cell seeding of ePTFE grafts. This method was applied clinically with good results. However, it has never found a wide clinical application.

In vitro tissue engineered vascular grafts using a degradable 3-D scaffold, seeded with different cells in a dynamic bio-reactor, or using the cell sheet technology, have been successful in experimental settings and in a very limited number of patients.

Other approaches of engineering tissue tubes in the peritoneal cavity have also been tried to recreate 3-layered vessels.

We have elected the method of in vivo tissue engineering by implanting a synthetic biodegradable vascular scaffold made of various medical grade polymers to induce appropriate autologous cell ingrowth in the scaffold in order to recreate a neo-artery during the degradation of the scaffold with simultaneous replacement by the native tissues. We manufactured the vascular prostheses with the method of electro-spinning which has been widely propagated by Bowlin to obtain a random, nano/micro-fiber 3D porous structure which mimics extra cellular matrix and shows the necessary mechanical properties to be used as an arterial replacement (Fig. 1). Several degradable polymers were evaluated for their mechanical properties, degradation, cell ingrowth and biocompatibility. However, due to aneurysm formation after arterial replacement in the rat infra-renal aorta, most of the short-term degrading polymers were abandoned and we concentrated on the use of poly(ε-caprolactone) (PCL) which degrades over a period of one to two years.

Using our electro-spin PCL scaffolds, we could obtain good results in the rat model up to six months and more with regard to surgical handling, patency, lack of aneurysm formation, endothelialization and cellular ingrowth, comparing favorably to the control ePTFE grafts (Fig. 2). Histologically, the scaffold shows homogenous cellular infiltration by macrophages and myofibroblasts, producing collagen and sparse...
Figure 1. Schematic drawing of electro-spinning. The insert shows the luminal surface of random nano/micro PCL fibres.

Figure 2. Implantation and angiography. (A) shows the operative site after completion of the prosthetic replacement of the rat abdominal aorta by a PCL graft. (B) Represents a contrast angiography of the patent abdominal aorta 6 months after graft implantation.
elastin fibers. Thus, the ingrown cells produce an autologous extracellular matrix. The luminal surface is covered in a confluent manner by endothelial cells as early as six weeks which is significantly faster and better than in ePTFE controls (Fig. 3). Intimal hyperplasia formation is moderate and mainly seen at both anastomoses, thus remaining an enemy of small caliber vascular prostheses and therefore we manufactured a drug-eluting vascular prosthesis. The drug paclitaxel was chosen since it showed successful reduction of intimal hyperplasia on stents. Our drug-eluting prosthesis showed a tri-phasic paclitaxel release in vitro and a significant reduction of intimal hyperplasia on stents. This was achieved with a significantly faster and better than in ePTFE controls (Fig. 3).

In conclusion, we could prove with our studies that the concept of successful vascular regeneration using an acellular degradable synthetic polymer is possible. Several questions remain open and require further investigation such as the fate of the initial vascular compliance after implantation and cellular ingrowth, the function of the neo-vessel after complete degradation of the polymer and the danger of initial thrombosis before complete endothelialization of the luminal side. However, the approach of in vivo vascular tissue engineering seems to be feasible and has some definite advantages over the in vitro cell and bio-reactor-based vascular graft engineering.

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