Development and application of electrospun supramolecular absorbable medical devices in preclinical to clinical trials

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Statement of Purpose: Despite a range of advances in electrospinning manufacturing, translation of electrospinning from a research technique to a medical device manufacturing process remains limited and have resulted in community skepticism, and in some cases complete abandonment of the technique. Xeltis, a clinical-stage medical device company, makes use of supramolecular chemistry together with state of the art electrospinning technology to develop off-the-shelf polymeric medical devices that allow Endogenous Tissue Restoration (ETR), a new transformational therapeutic approach in cardiovascular treatment. The goal of ETR is to enable the body's natural healing process to pervade the devices with components of native tissue, including collagen, endothelial lining and capillary blood vessels, which normally develop and organize into natural functioning tissue. The matrices are structured to be absorbed over time, to leave patients with new, healthy tissues. The innovative combination of supramolecular polymer properties with electrospinning manufacturing technique has been verified in preclinical and clinical trials.

Methods: Large diameter grafts were developed and tested for safety & functionality as pulmonary interposition grafts in an ovine model with a follow-up of up to 1 year [1]. This data, together with ISO-10993 biocompatibility testing laid the foundation for a clinical feasibility trial using the large diameter graft in a Fontan procedure in 5 single-ventricle pediatric patients. In parallel, the large diameter grafts were developed into valved conduits by adding leaflets. The valved conduits were implanted in the pulmonary position in sheep and followed for a maximal period of 2 years. All devices were manufactured using the electrospinning technique with a view to achieve ETR. In line with ISO standards, product specifications were rigorously defined and controlled throughout manufacturing, including control of device absorption and mechanical properties. Electrospinning was selected as the primary manufacturing technique to provide necessary physical features to permit cell infiltration of the device and substitution with natural tissue by ETR.

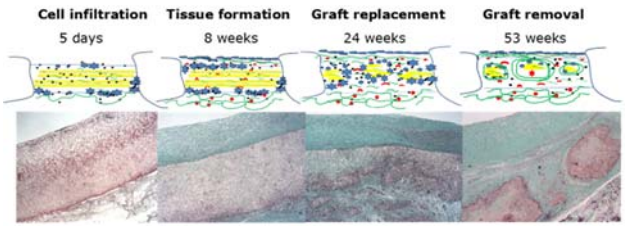

Figure 1: Various stages of ETR in non-valved pulmonary conduits in sheep (Masson-Trichrome, collagen showing in green). Adapted from [1].

Results: The non-valved pulmonary interposition grafts in the sheep model demonstrate safety as well as the different phases in the ETR process [Figure 1], while diameters were stable throughout follow-up. Recently, we reported successful 2-years follow-up with 5 patients that were implanted with our bioabsorbable electrospun graft in a modified Fontan procedure [2]. There were no signs of dilation or stenosis [Figure 2, left] with no device-related adverse events to date.

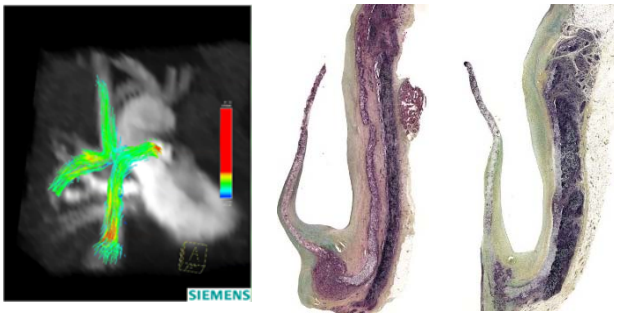

Figure 2 Clinical conduit and pre-clinical valved conduit. Left: MRI frontal image and 4D Flow at 26 months follow-up showing good patency and flow dynamics of Fontan conduit in a single-ventricle patient ([2]). Middle and right: Histology showing ovine PV conduits after 6 (middle) and 12 months f-up [right]. Adapted from [3].

Based on the results of PV conduits implanted in sheep for up to 2 years [3], enrollment was started in the XPLORE-1 clinical trial, and successful implantation in first 3 patients was recently reported [4].

Conclusions: We report on the preclinical and clinical development of two off-the-shelf bioabsorbable medical devices based on electrospinning in combination with supramolecular chemistry. The results presented here confirm the potential of synthetic bioabsorbable polymers to induce Endogenous Tissue Restoration, without the need for additional growth factors or bioactive peptides. Continued success could represent a paradigm shift in the approach to cardiovascular regeneration strategies.

References:

[1] Schoen et al (2016), Vascular remodelling of a novel absorbable polymeric conduit in the ovine pulmonary circulation, Poster presented at WBC, Montreal.
[2] Bockeria et al (2016), A novel bioabsorbable vascular graft in modified Fontan procedure - mid-term results, presented at EACTS, Barcelona
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[4] Prodan et al (2016), First ever bio-absorbable heart valve implantation, presented at EACTS, Barcelona