Topics Covered

- Artificial Blood Vessels : Introduction, history and Significance
- Strategies for Bio-engineering of Blood Vessels
- Cell Assembled Grafts, De-cellularized Tissue and Pre-Fabricated Grafts
- Materials for Bio-engineering of Blood Vessels
  - Natural and Synthetic Polymers
- Fabrication Techniques
  - Electrospinning
  - Thermal Induced Phase Separation
  - Braiding
  - 3D-Printing
- Ex-vivo formation of Blood Vessels
- Commercially Available Artificial Blood Vessels

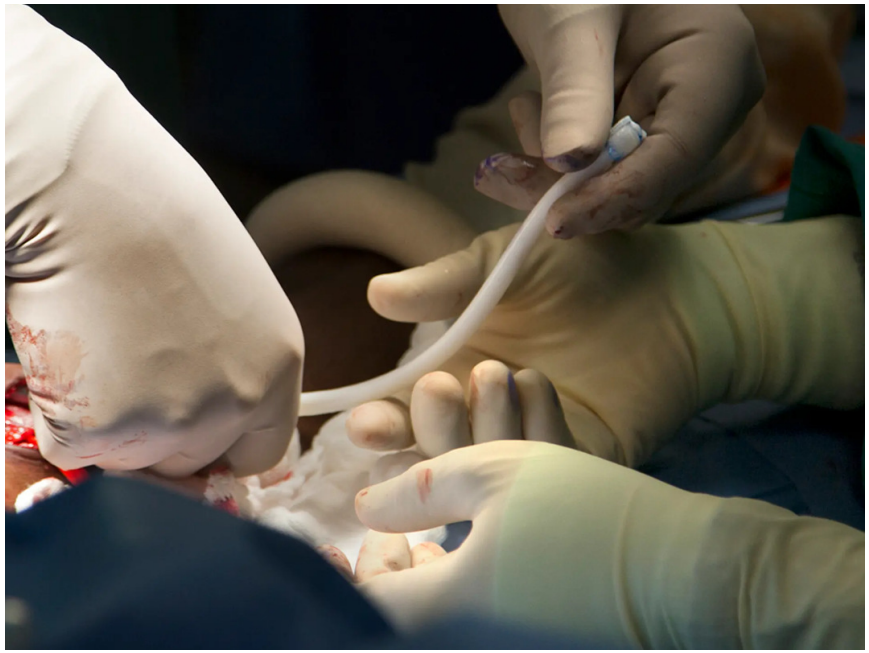
Artificial Blood Vessels

- Artificial blood vessels are important type of medical textile materials, and are mainly inserted into an existing artery.
- The first artificial blood vessel model was developed by Weinberg and Bell in 1986 (published in *Science*). It consisted of a multilayered, Dacron mesh-integrated, collagen scaffold seeded with smooth muscle cells.
- Tissue engineering technology combines cells, tissue scaffold, and engineering in order to generate vascular grafts. Particularly creation of small-diameter artificial blood vessels has progressed well in terms of employing tissue engineering techniques through different approaches, such as artificial blood vessels using biodegradable polymers as scaffolds or consisting of decellularised vascular tissue.
- Novel approaches have been used to construct (Tissue-Engineered Vascular Grafts) TEVGs for clinical use and these have been demonstrated to have many advantages, such as three-dimensional (3D) bioprinting, which allows for the use of autologous cells alone without any scaffolding in the preparation of different sized small-diameter artificial blood vessels.

Significance of Artificial Blood Vessels

- Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, affecting approximately 523 million people. The most common cause of CVD is atherosclerosis, the buildup of fatty plaques within arterial walls, which leads to blockages and reduced blood flow to downstream tissues.
- Vascular grafts are mainly used for the surgical treatment of vascular diseases that require new long-term revascularisation, including abdominal aortic aneurysms, coarctation of the aorta and chronic haemodialysis access.
- A single vascular graft often is taken as an autologous graft from the patient, which is commonly the saphenous vein from the leg or the internal thoracic artery from the chest wall.

.

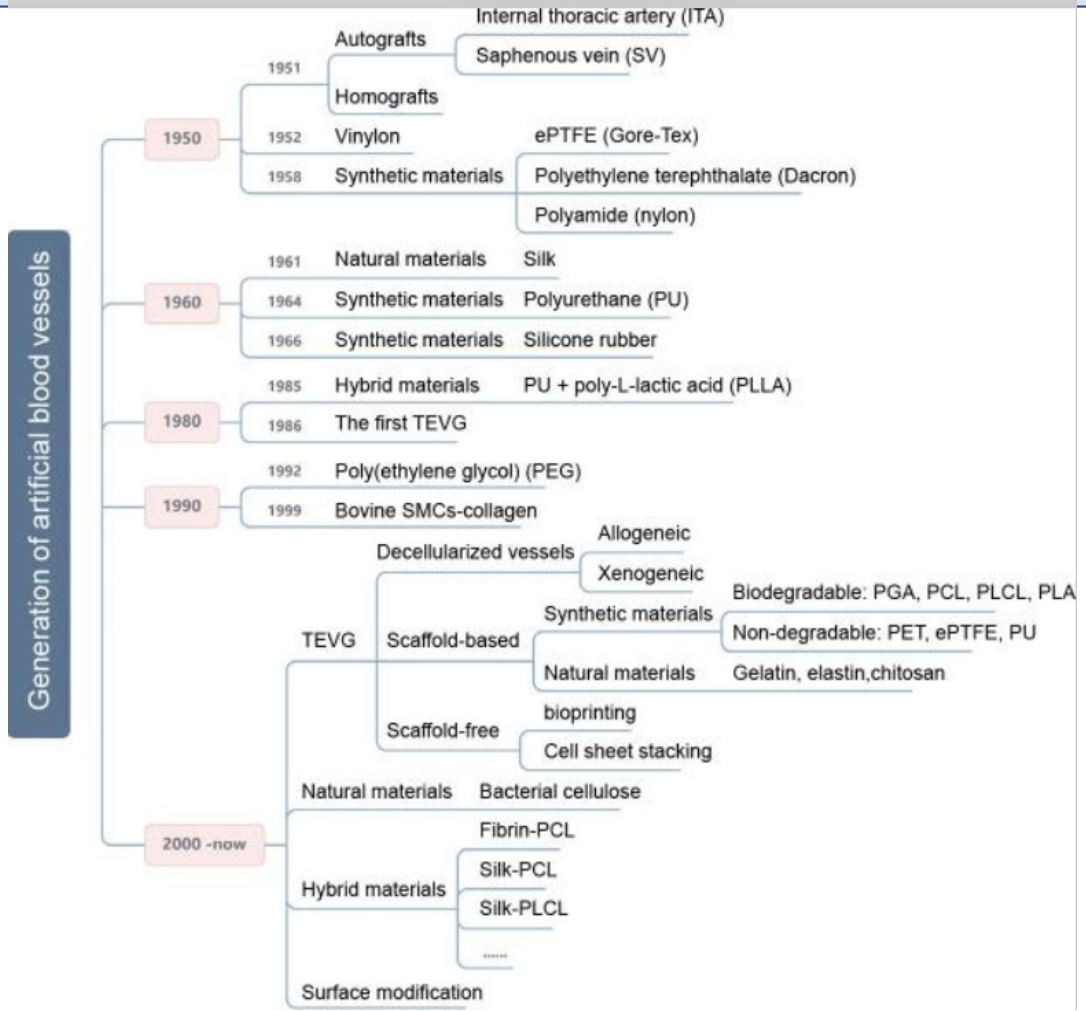


Surgeons at Duke University implant a bioengineered blood vessel in a kidney dialysis patient

Significance of Artificial Blood Vessels

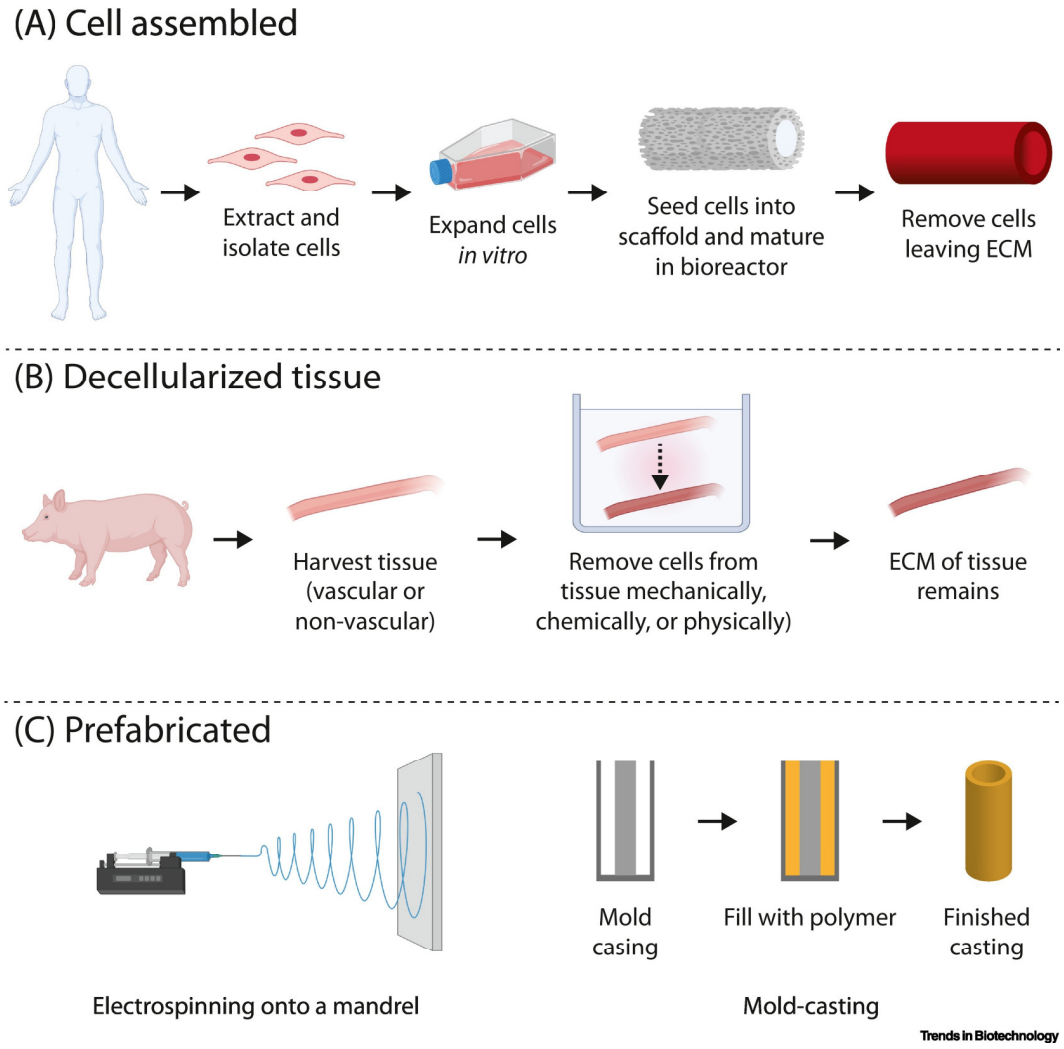
- However, autologous blood vessel availability is limited and requires invasive harvesting techniques. Moreover, with passage of time, the quality of autologous blood vessels can be difficult to guarantee, and the incidence of postoperative complications is higher.
- Therefore, it is of great clinical significance to obtain vascular prosthetics that can function as blood vessels in order to restore blood flow around a blockage or replace damaged blood vessels
- Various types of materials are used to prepare artificial vascular grafts, including synthetic polymers, natural materials, or a mixture of types. In addition, there is increasing interest in regard to the development of tissue-engineered vascular grafts (TEVG) among various other approaches, which are currently under investigation.
- There is increasing interest in regard to the development of tissue-engineered vascular grafts (TEVG) among various other approaches.

Timeline of Artificial Blood Vessels



A few significant time points in the generation of artificial blood vessels and the main research areas are shown.

Strategies for Bio-engineering of Blood Vessels

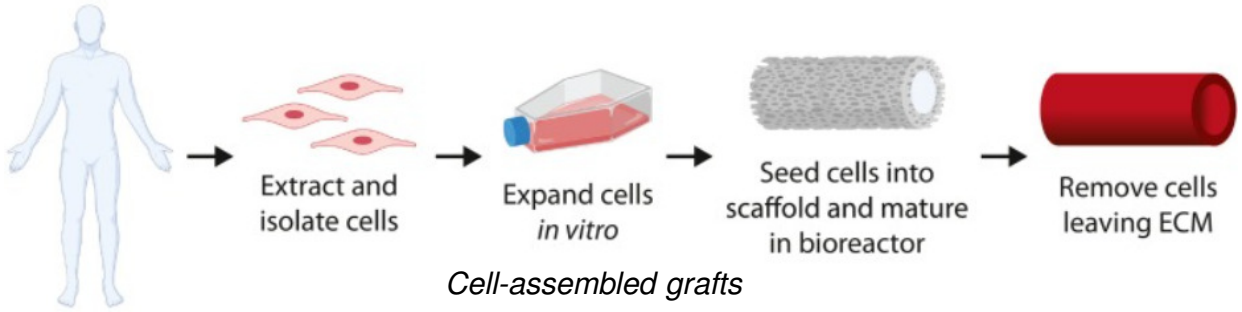


- To date, a number of fabrication techniques have been adopted to create clinically-viable TEVGs which vary widely in terms of materials, manufacturing methods, cell sources, and culture protocols. There are three common strategies for bioengineering artificial blood vessels that have dominated research efforts cell-assembled, decellularized tissue, and fully prefabricated grafts.

(A) Cell-assembled grafts are composed of *de novo* extracellular matrix (ECM) deposited into a degradable polymer scaffold by cells during extended culturing. (B) Decellularized tissue grafts are derived from the ECM of native tissue harvested from animal or human cadaveric source. (C) Prefabricated grafts are constructed from synthetic or naturally derived polymers using techniques such as electrospinning, mold-casting, or freeze drying.

Cell-assembled Grafts

- Cell-assembled grafts are composed of *de novo* extracellular matrix (ECM) deposited by cells during extended culturing.
- Cells are extracted from a patient or donor and the desired cell type (can be range of human cell types such as Smooth Muscle Cells, fibroblasts, and induced pluripotent stem cells) is isolated and expanded *in vitro*. Cells are then seeded into a degradable porous scaffold that provides a three-dimensional template of the final graft. The cell/scaffold construct is then cultured in a bioreactor system for several weeks, during which time the cells simultaneously degrade the scaffold whilst depositing new proteins that form the final graft structure.
- Pulsatile blood flow may be simulated during cell culture to mechanically condition the construct. Finally, the construct is decellularized prior to implantation to remove cellular antigens that could provoke an immune response. This approach is resource and time intensive, making production expensive, with a high regulatory burden.
- Cell-assembly strategies have both the highest complexity and degree of biomimicry, with variations developed using an array of human cell types (SMC, fibroblasts, and induced pluripotent stem cells) cultured for long periods to produce *de novo* conduits.



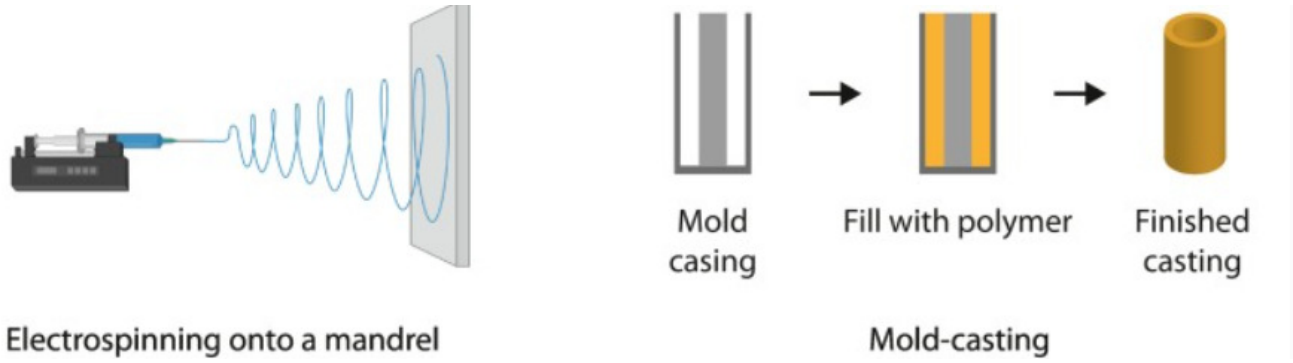
Cell-assembled grafts

De-cellularised Tissue

- Decellularized tissue grafts are derived from the ECM of native tissue harvested from animal or human cadaveric source. Tissues previously used for harvest include blood vessels, small intestinal submucosa, the ureter, and amnionic membrane. Cells and cellular material are removed from the tissue to reduce immune reactivity.
- Tissue decellularization strategies may be chemical (detergents and solutions of different pH and tonicity), biological (DNase and RNase enzymes), and/or physical (pressure treatments, sonication, and freeze–thaw cycles).
- Decellularization benefits from leveraging some elements of the native tissue structure, but grafts generated using this approach have poor blood interaction due to the high collagen content and are subject to ongoing regulatory issues.
- Decellularized tissue-based grafts aim to exploit the architecture and mechanical properties of vessels derived from animal and human cadaveric tissue, removing cells before use to reduce harmful immune reactions. These grafts are available for clinical use, though have not been widely adopted.
- Clinical performance has been limited by high rates of thrombosis, infection, and rapid degeneration leading to aneurysm formation.

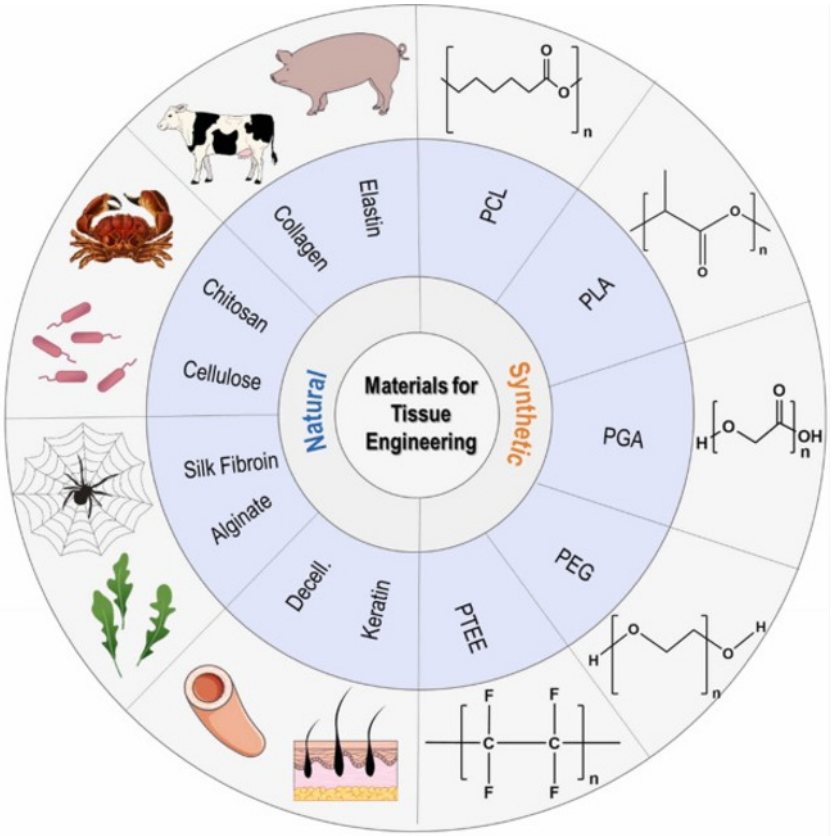
Pre-Fabricated Grafts

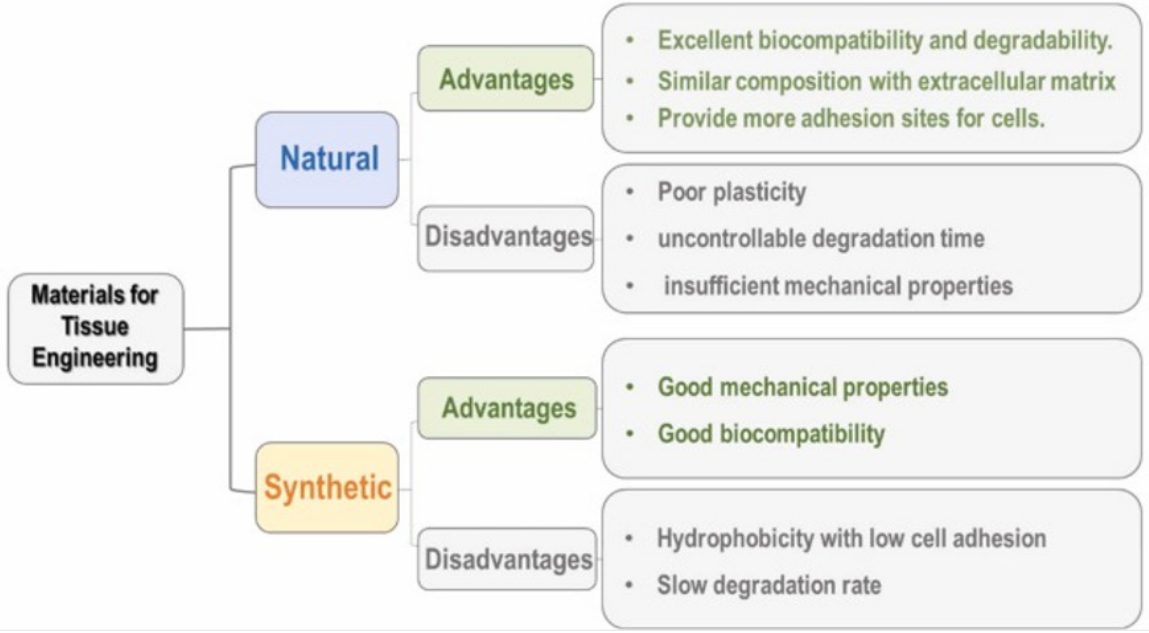
- Prefabricated grafts are constructed from synthetic or naturally derived polymers, or a hybrid.
- Common manufacturing techniques include electrospinning, mold casting, knitting or braiding, gel-spinning, and freeze drying. This mode of production has the lowest level of biomimicry; the only materials to reach the clinic are polymers without any biological cues.
- However, they also have the lowest regulatory burden and can be compatible with scaled production, sterilization, and off-the-shelf use.



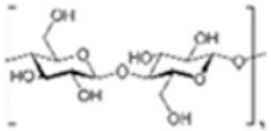
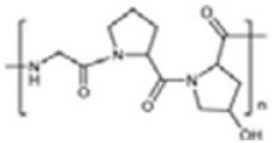
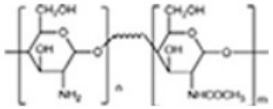
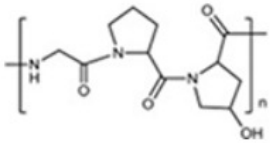
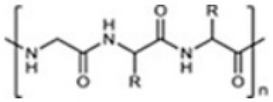
Pre-fabricated grafts

Materials for the Bio-engineering of Blood Vessels

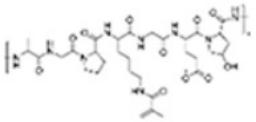
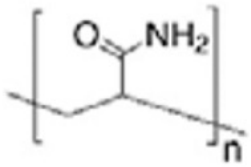
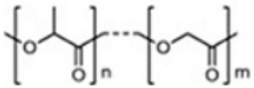
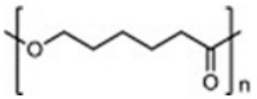
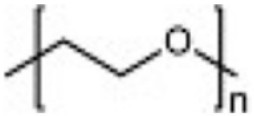
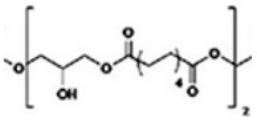




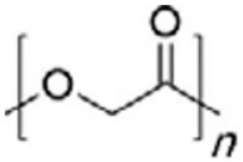
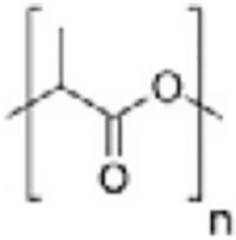
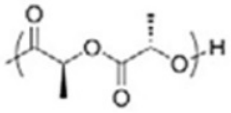
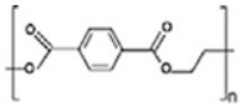
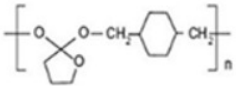
Natural Polymers

Natural Polymers	Chemical Structures	Main Advantages & Applications
Cellulose		Mechanical properties,[34] shape-memory, self-rolling[26]
Collagen		Cell adhesion,[35] elastic modulus,[31] hydrogel[7]
Chitosan		Cell encapsulating[6] surface modification[37]
Gelatin		Cell growth,[38] cell proliferation,[30] hydrogel,[39] ECM[40]
Silk		Biocompatibility,[41] compliance,[42] hydrogel[43]

Synthetic Polymers

Synthetic Polymers	Structural Units	Main Advantages & Applications
Gelatin methacrylate (GelMA)		Hydrogel,[44] cell encapsulation[45]
Polyacrylamide (PAM)		Hydrogel[43]
Poly (D,L-lactic acid-co-glycolic acid) (PLGA)		Tissue engineering and biocompatibility,[46] cell affinity[47]
Poly (ε-caprolactone) (PCL)		Tissue engineering[13,48,49]
Poly (ethylene glycol) (PEG)		Surface modification,[50] biocompatibility[51]
Poly (glycerol sebacate) (PGS)		Elastomer[52,53]

Synthetic Polymers

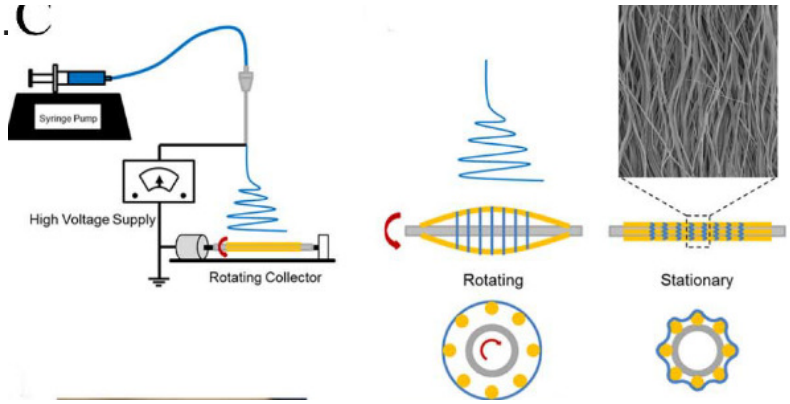
Polyglycolic acid (PGA)		Thermoplastic polymer[54]
Polylactic acid (PLA)		Mechanical properties,[55] tissue engineering[56]
Poly (L-lactic acid) (PLLA)		Mechanical properties,[55] tissue engineering[56]
Polyethylene terephthalate (PET)		Biofabrication[8]
Polyorthoester (POE)		Mechanical properties[57]

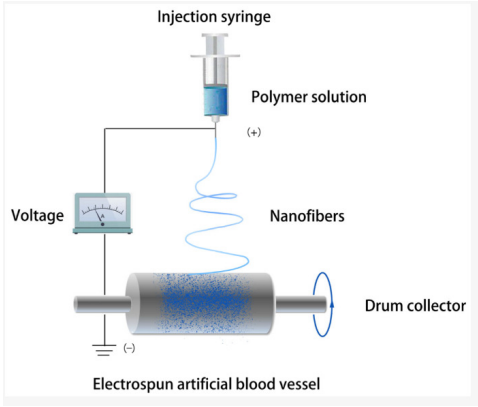
Fabrication Methods-Electrospinning

- With developments in science and technology, the materials and structures of artificial blood vessels have been continuously improved, and the preparation processes of artificial blood vessels have also been gradually enhanced. Preparation technologies include electrospinning, thermal phase separation, braiding, 3D-printing.
- **Electrospinning:**

Electrospinning is a process in which a polymer solution or melt is used to form a small jet of polymer under the action of a high-voltage electrostatic field for spinning. Electrospinning enables the direct and continuous preparation of polymer nanofibers. Typical electrospinning equipment consists of a syringe pump, collector, and high-voltage supply.

By using a customized electrospinning collector, a vascular graft with a layered, circumferentially aligned, and micro-wavy fibrous structure similar to natural elastic tissues can be fabricated.





Thermal-Induced Phase Separation

- **Thermal-Induced Phase Separation:**

The principle of TIPS is to phase separate a polymer–solvent or polymer–solvent–non-solvent homogeneous solution by cooling it to a low temperature to introduce polymer-rich and polymer-lean phases.

After induced phase separation, the solvent is removed by extraction, evaporation, or freeze drying, and pores are formed in the remaining solid phase due to solvent removal. There are two typical TIPS mechanisms; namely, solid–liquid phase separation and liquid–liquid phase separation.

TIPS has been adopted to construct biodegradable scaffolds including blood vessel grafts. A micro-tubular orientation-structured blood vessel mimicking a natural structure was prepared by an improved TIPS technique.

Braiding

- **Braiding:**

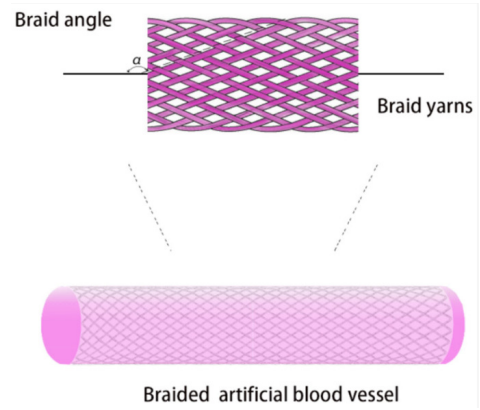
Braiding is a process of winding three or more fiber yarns in a specific pattern along the direction of fabric formation. The low bending stiffness of the braided tube, and the ease of compression and recoil of the braided structure, make them promising candidates.

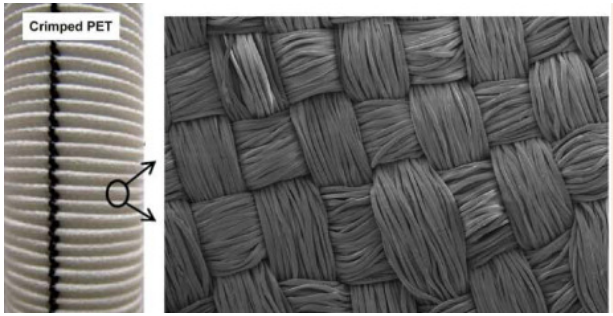
the required stitching of the tubular graft limits the movement of the constituent lines at their intersection, the braided graft has not been very successful in endograft applications.

Thus, the concept of using a multi-layer weave design has been introduced to reduce the porosity of the graft while maintaining flexibility, and it has been used to make novel vascular grafts.

Preparation of artificial blood vessels by braiding technology improves elasticity and compression resistance, and enhances the compliance of the blood vessels.

Braiding technique is often used to improve the strength of anastomosis while ensuring the flexibility of the inner layer material through the design of a multi-layer artificial blood vessel.





3D Printing

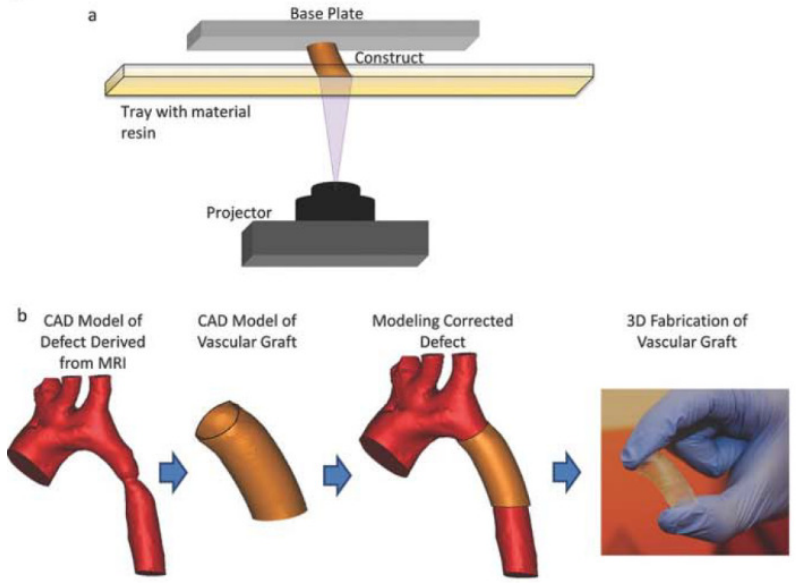
- **3D Printing:**

3D printing technology appeared in the mid-1990s and is based on digital model files, using powdered metal or plastic materials to construct objects through a layer-by-layer printing method.

Due to the quickly customizable and personalized organ-like products created by 3D printing or bioprinting, more attention has been paid to using it.

Three-dimensional printing is a promising tool for generating tissue-engineered scaffolds using different target cells in biocompatible materials (e.g., hydrogels).

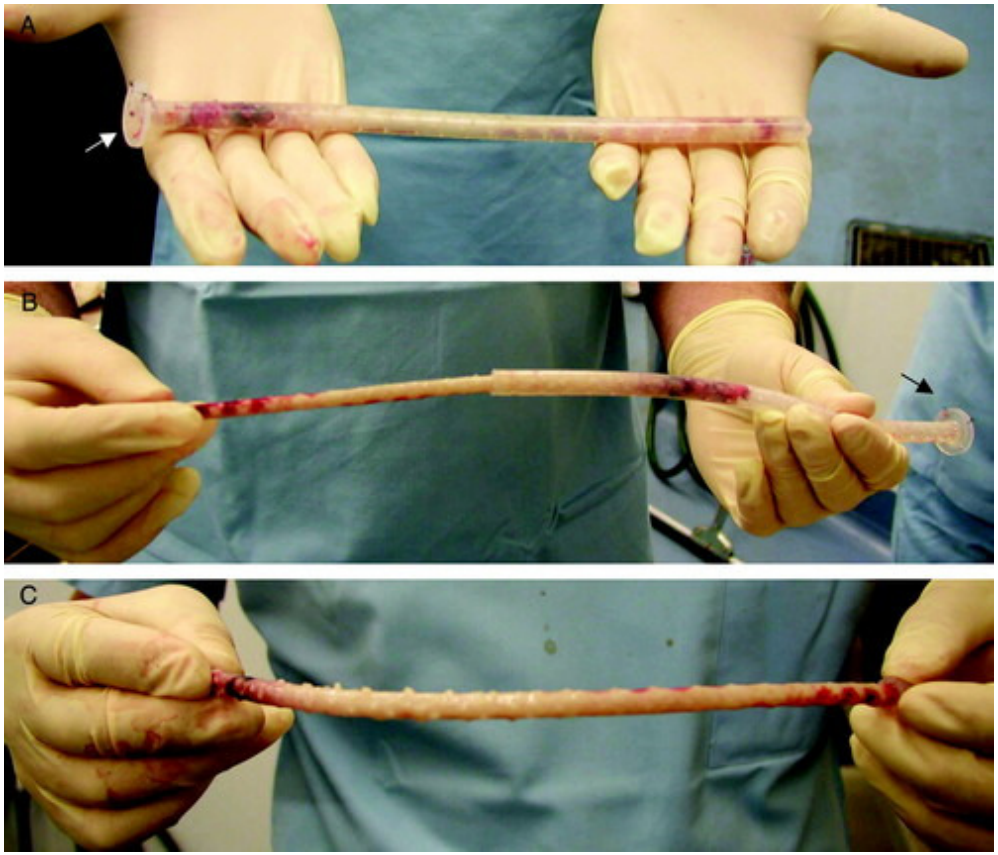
However, 3D printing has not been directly applied to the generation of patient-specific coronary artery bypass grafts. Most studies have focused on the *in vitro* production of vascular models and the lining of endothelial cells on the inner surface; in particular, the formation of microvascular networks to study angiogenesis and thrombosis or the supply of nutrients and oxygen to engineered tissues.



Ex-Vivo Formation of Blood Vessels

Tissue-Engineered Blood Vessels
Alternative to Autologous Grafts?

Michel R. Hoenig, Gordon R. Campbell, Barbara E. Rolfe, Julie H. Campbell



A. "Device" within which the tissue capsule has grown over 2 to 3 weeks in the peritoneal cavity of the dog. Cells floating in the peritoneal fluid have entered the "device" through holes in the sheath and formed a tissue capsule around an inner tube, whose diameter can be varied. The outer surface of the sheath had been coated with surfactant to prevent adhesions. The "device" was inserted (distal end first) through a 2- to 3-cm incision in the skin of the abdomen and a smaller incision in the underlying peritoneal wall and the flange (arrow) positioned on the outer surface of the peritoneal wall. Purse-string sutures sealed the peritoneal incision and 3 loose sutures held the flange in place, and then the skin incision closed. For harvest, an incision was made in the skin, the flange sutures were cut, and the "device" was slid out, followed by closure of the incisions.

B. The tissue capsule and inner tube are removed from the outer sheath by cutting around a tab at its distal end and sliding them out.

C. The tissue capsule can then be slid off the inner tube.

DOI: 10.1161/01.ATV.0000158996.03867.72

Commercially Available Artificial Blood Vessels

Commercially-available artificial blood vessels in clinical use.

Company	Product name	Material	Details and modification	Indications for use
Atrium Medical Corporation	Flixene IFG Vascular graft	ePTFE	Very strong and durable with three layers	Arterial vascular reconstruction/segmental bypass/arteriovenous vascular access
Bard Peripheral Vascular, Inc.	Venaflo™ II Vascular graft	ePTFE	Cuffed to promote good hemodynamic performance	Subcutaneous arteriovenous conduits for blood access only
Edwards Life Sciences	Edwards Lifespan reinforced expanded PTFE vascular graft	ePTFE	Higher crush and kink resistance	Bypass or reconstruction of diseased or occluded blood vessels/arteriovenous shunts
Maquet Cardiovascular, LLC	FUSION Vascular Graft	ePTFE	Two layers fused with a proprietary polycarbonateurethane adhesive	Peripheral artery repair or replacement/vascular access
	FUSION™ and FUSION™ Bioline	ePTFE and PET	Two layers with heparin/albumin coating on the interior surface	Peripheral artery repair or replacement

Commercially Available Artificial Blood Vessels

Commercially-available artificial blood vessels in clinical use.

Vascutek Ltd.	Vascutek Gelsoft Plus ERS Vascular Graft	PET	External polypropylene support, gelatine-sealed, knitted polyester grafts	Indicated for extra anatomical vascular repair, primarily for axillo-femoral/bi-femoral bypass and femoropopliteal reconstruction
	Vascutek Gelseal™ Vascular Grafts	PET	Knitted, gelatine impregnated	Indicated for replacement or bypass of abdominal arteries afflicted with aneurysmal or occlusive disease
	Vascutek Gelsoft™ Vascular Grafts	PET	Knitted, gelatine impregnated, zero porosity	Indicated for abdominal and peripheral vascular repair
	Vascutek Gelsoft™ Plus Vascular Grafts	PET	Knitted, gelatine impregnated, dilation resistant	Indicated exclusively for abdominal and peripheral vascular repair
W.L. Gore & Associates, Inc.	Gore-Tex	ePTFE	Unmodified	Vascular access
	Gore-Tex Stretch	ePTFE	Stretch	
	Gore Propaten	ePTFE	Reduced thrombogenicity	