Mini Review

The Eve of commercialization: Decellularized vascular matrix as small-diameter blood vessel

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Abstract

Over the past three decades, the field of tissue engineering has advanced rapidly and become a research hotspot in biomedicine, especially for treating the damages caused by cardiovascular diseases. Although artificial blood vessels with excellent functionality have been developed through advanced technologies, the use of tissue-engineered small-diameter vascular grafts for treating cardiovascular diseases has not been explored in depth. Decellularized vascular matrices for small-diameter vascular grafts offer unique advantages as they retain the entire extracellular matrix, have superior biocompatibility, and cause minimal immunogenic reactions. Therefore, many corporations around the world are trying to develop decellularized vascular matrices into viable vascular grafts that could be commercially used. Here, we briefly introduce four eminent companies that have undertaken this challenge and their representative products, including Cytograft Tissue Engineering Inc., Humacyte, Inc., Vascudyne, Inc. and LeMaitre Vascular, Inc.

Introduction

Currently, cardiovascular diseases are the leading global cause of morbidity and mortality [1]. In the European Union (EU), the number of deaths caused by cardiovascular diseases in 2020 exceeded 3.9 million, accounting for 45% of total annual deaths [2]. As of now, although bypass grafting using autologous vessels remains the gold standard for coronary artery bypass grafting (CABG), this approach has several drawbacks. On account of peripheral vascular diseases and other reasons, not all patients have good autologous blood vessels to meet the requirements of autologous transplantation. Therefore, there is an urgent need for a safe and efficient vascular repair technique that can be applied in clinical practice. In addition to their application in treating cardiovascular diseases, vascular grafts are also widely used in the treatment of other conditions such as end-stage renal diseases (where patients require arteriovenous shunts for hemodialysis). In addition, vascular repair technique would also be useful in other conditions like peripheral vascular injuries caused by trauma, or atherosclerosis of the lower extremities, both of which need peripheral vascular bypass grafting.

Non-resorbable synthetic vascular grafts demonstrate good patency rates and long-term performance for the replacement of the aorta and larger arteries; however, they perform poorly when used for small diameter (< 6 mm) blood vessels with high rates of infection and thrombosis. In recent years, the field of tissue engineering has advanced rapidly. Within this field, the development of artificial blood vessels with good functionality has become a research hotspot in biomedicine. Globally, several firms are trying to develop decellularized vascular matrices as small-diameter vascular grafts for commercial use. Here, we briefly discuss several well-known corporations, namely, Cytograft Tissue Engineering Inc., Humacyte, Inc., Vascudyne, Inc. and LeMaitre Vascular, Inc., and the vascular graft products that they have developed or are in the process of developing.

Cytograft Tissue Engineering Inc.

Cytograft Tissue Engineering Inc. was one of the first companies to develop artificial vessels. The idea of developing ‘human textiles’ was based on early research into the use of cell sheet engineering to reconstruct artificial vessels [3]. This approach relied on using endothelial cells and fibroblasts extracted from small biopsy samples of skin and superficial veins, and producing fibroblast sheets in as little as 6 weeks. The tissue-engineered vascular grafts consisted of three components: a living adventitia, a decellularized internal membrane, and endothelium [4]. However, this procedure

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can cost > 15,000 USD and patient-specific vascular grafts can take up to 6-9 months to produce. Due to these reasons, it is unlikely that this approach will become standard clinical practice. However, the preparation methods used by this company have provided new avenues for research on producing artificial vascular grafts.

**Humacyte Inc.**

Humacyte, Inc. was founded by Laura E. Niklason from Yale University in 2004 to develop innovative technologies for regenerative vascular medicine. The company focused on a new type of tissue-engineered vessel known as ‘human acellular vessels’ or HAVs [5] (Figure 1). HAVs are completely decellularized and mechanically robust with circumferentially aligned extracellular matrices without any chemical cross-linking or synthetic components [6]. They are favorably repopulated by host cells in multiple advanced-stage clinical trials of vascular trauma repair, arteriovenous access for hemodialysis, and peripheral arterial disease. Combined with the FDA’s Expanded Access Program (EAP), which includes eight clinical trials, the HAVs have been implanted in > 500 patients to date. The corporation is currently conducting three phase-3, one phase-2, and three phase-1 clinical trials worldwide [7,8] (Figure 2).

**Vascudyne, Inc.**

Vascudyne, Inc. was founded by Jeff Franco and Kem Schankereli. It licensed its proprietary TRUE Tissue technology, which was developed by Professor Robert Tranquillo and his colleagues from the University of Minnesota in 2017 (Figure 3). Currently, the company produces several products under its TRUE™ Tissue line, including TRUE™ Graft, TRUE™ Valve, and TRUE™ Patch [9]. The TRUE™ Graft has biological and mechanical properties that are very similar to native tissues and is based on the results from preclinical studies. It is expected to regenerate, grow, and integrate into the implant site. Vascudyne, Inc. announced the successful first-in-human use of its TRUE™ Vascular Graft for patients with an end-stage renal disease requiring hemodialysis access in July 2021.

**LeMaitre Vascular, Inc.**

Artegraft® is a bovine carotid vascular graft approved by FDA in 1970. Its decellularized matrix is treated for use as hemodialysis access and lower extremity bypass. Its biological fibrous matrix is processed to enhance long-term patency and provide a tightly woven, cross-linked conduit that is flexible and compliant. LeMaitre Vascular, Inc. acquired the business and assets of Artegraft, Inc. for 90 million USD in 2020. For the last 50 years, Artegraft has been implanted in > 500,000 patients.

In Oct 2020, Hancock Jaffe Laboratories, Inc. (HJLI) announced that the first heart bypass surgery in HJLI’s first-in-human CoreoGraft study was completed and that the patient was discharged from the hospital. In May 2022, Medical 21 Inc. announced the development of an artificial graft called the ‘MAVERICS’ graft, a small-diameter flexible tube encased in a nickel-titanium alloy stent, which eliminates the need to harvest blood vessels from the patient’s legs, arms, and chest. The goal of the MAVERICS graft is to improve a patient’s quality of life by reducing pain, shortening surgery and recovery times, and reducing the risks of infections and complications.

**Conclusion**

The efforts of the four representative companies mentioned in this study show that the use of decellularized vascular matrices as vascular grafts is commercially viable. Commercializing the use of vascular grafts has been and continues to be a tortuous and arduous journey, and its regular clinical application is still at an emergent stage. The research and development stages and clinical trials are not yet complete for most vascular graft products under development. However, as the technology for producing vascular grafts is improving and advancing steadily through the active efforts of worldwide research, the field is expected to become commercially viable very soon.
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Authors’ contributions

Yuanming Li conceived the review and wrote the manuscript. Dr. Nianguo Dong helped edit the text. Dr. Xuefeng Qiu contributed to the conception of the study. All authors contributed to the article and approved the submitted version.

References


