A Clinical Commentary on the Article “EMT-Inducing Biomaterials for Heart Valve Engineering: Taking Cues from Developmental Biology”

Clinical Utilization of Tissue-Engineered Heart Valves—Meeting Today's Standard

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Attempts to engineer a heart valve substitute have been performed over the last two decades with significant progress achieved in cell biology, biomaterial composition, and biomechanical stimulation. Application of tissue-engineering techniques has become clinically relevant in urology, orthopedics, plastic surgery, and otolaryngology, treating defined pathologic entities which improve patient's quality of life and clinical practice [1]. From an epidemiologic standpoint, clinical relevance of tissue-engineered valves could affect millions of patients annually and alter the treatment algorithm for patients with both acquired and congenital valvar disease [2].

This manuscript offers insight into future biomaterials development utilizing techniques and advancements individually investigated. Combining the optimal mechanical properties achieved with electrospinning with biologic properties that support endothelial cell to mesenchymal cell transformation, a directed, possibly programmed, construct is plausible and the forefront of biomaterial design.

Tissue-engineered constructs have a formidable task to meet and surpass current valve technology. While many cite the need for anticoagulation, the risk of calcification, limited durability, and the lack of growth potential as limitations, industry has made significant progress in mitigating these barriers. The stented bioprosthesis is the

most utilized valve in clinical practice and has a low risk of thrombosis and thromboembolism. In most positions, the American Heart Association recommends an antiplatelet agent for anticoagulation, most often in the form of aspirin [3]. Anticalcification agents are proprietary for each valve and have improved with each generation of production. While data are being accrued, current short- and long-term follow-ups using both pericardial and porcine tissue valves show improved rates of calcification. Bioprosthetic valve durability has improved with each generation of valve design. Recent studies have shown maintenance of hemodynamics and bioprosthetic function up to 20 years in older patient cohorts [4].

The possibility of tissue-engineered heart valve growth with patient maturation could dramatically impact patient care. Valve companies have directed design and development effort to create catheter delivery systems with implantation in the pulmonary and aortic positions in the early stages of becoming accepted practice [5, 6]. By creating a stented valve that is expanded to conform to multiple defined size ranges, industry has created the first adjustable implant. As initial implants evaluate technique and efficacy, future investigation will include continued stent dilation and valve expansion as would be required for developing stenosis in the setting of somatic growth. Additionally, the less invasive techniques will impact re-operative open valve surgery. Clinical trials are being designed using catheter-inserted valves to replace previously placed valves in both the aortic and pulmonary positions (valve-in-a-valve concept) [7].

Current industry standards are elevating the benchmark required for clinical application of tissue-engineered heart valves as we continue to understand biologic principles

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and technical requirements. To compete with current valve technology, engineered valves will be required to have fluid leaflet function with complete central coaptation. They will need to remain competent when exposed to pressures in either the systemic or pulmonary circulation and approximate the effective orifice area of size-matched native valves. Long-term risk of thrombosis and thromboembolism should be negated by the presence of a functional endothelial surface. Implantation should be easy, and valve sterility must not be compromised with infection rates similar to native heart valve endocarditis. Grossly, engineered valves should have physical characteristics maintaining geometry while handling and have tissue integrity to hold sutures and provide hemostasis. Microscopically, the tissue would be cellularized and have a three-layered architecture composed of collagen, glycosaminoglycans, and elastin in proportion to native valve extracellular matrix. The clear advantage of tissue-engineered valves is the ability to grow and remodel. Patients with congenital heart valve disease could be spared multiple valve-related procedures and shift the manner in which they receive their care.

Industry will continue to improve upon the current standard. Autologous tissue-engineered heart valves maintained by endogenous biological cues are a significant stride in creating the ideal replacement. Understanding cell biology and biopolymer interaction is needed for continued

advancement, but exceeding current valve technology is required for clinical application.

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