Heart Valve Tissue Engineering and Regeneration
A Pathologist's Point of View
Frederick J. Schoen, M.D., Ph.D.
Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

The Rationale: Surgical repair or replacement of a diseased heart valve is common (85,000 per year US; 285,000 worldwide) yet presently available repairs and substitutes provide imperfect functional restitution, are not living tissue and have potential complications such as thrombosis, infection and degeneration (particularly calcification and extracellular matrix [ECM] damage for tissue valves). Moreover, pediatric applications require very small sizes, and multiple re-operations may be needed to accommodate patient growth, even if prosthesis-associated complications are prevented. Tissue engineered heart valves (TEHV) may overcome the limitations of contemporary valve substitution by creating or regenerating a living valve replacement that has good hemodynamic function, capacity to repair ongoing tissue damage, and long-term durability and growth potential similar to the natural heart valves.

Learning from Nature: Heart valves have a highly adapted and complex microscopic architecture with three cellular tissue layers, each enriched in a different ECM component: *fibrosa* -- collagen fibers provide strength and stiffness; *spongiosa* --- abundant glycosaminoglycans accommodate the internal rearrangements of the cusp ECM during the cardiac cycle; and *ventricularis* -- elastic fibers provide recoil. This permits the cusps to have minimal surface area when the valve is open and stretch without prolapse in response to backpressure of blood in the closed phase. Valves are lined by a confluent layer of *valvular endothelial cells* (*VECs)*; deep to the surface are abundant *valvular interstitial cells* (*VICs*).

The principal determinant of valve durability is the valvular ECM, whose quantity and quality depend on VIC viability and function. VICs synthesize the valvular ECM molecules and mediate ECM remodeling and repair. In normal adult valves, under equilibrium conditions, VICs are quiescent fibroblast-like cells, and VIC turnover and activation are low. Altered mechanical loading (e.g., in valve development, adaptation to changes in the local mechanical environment and in pathologic states), stimulates VIC activation resulting in ECM remodeling. VICs return to a quiescent state when mechanical equilibrium is restored.

Learning from Success and Failure: The design criteria for tissue engineered heart valves (TEHV) derive from five concepts established from studies of developing and diseased heart valves, and functioning as well as failed bioprosthetic valves**,** and other tissue valve substitutes: 1) The highly specialized arrangement of collagen and other ECM components of heart valves enables both optimal function and extended durability. 2) The quality of valvular ECM depends on the ability of VICs to modulate their phenotype and mediate valvular remodeling to adapt to different environments. 3) Structural deterioration of native and substitute valves occurs through chemical and mechanical damage to collagen. 4) Cell viability in chemically pretreated bioprosthetic and other tissue valve substitutes is compromised or eliminated during processing; thus, ECM damage that occurs following implantation cannot be repaired. 5) The long-term success of a TEHV will therefore depend on viable cells that can repair structural injury, remodel ECM, and potentially mediate growth.

Where the Technology is Now: In the general paradigm of tissue engineering, cells are seeded on a synthetic or natural biomaterial *scaffold* and then a tissue is matured *in vitro* (in a *bioreactor*) to form a *construct*. In the second step, the construct is implanted in the appropriate anatomic location, where further remodeling *in-vivo* may occur to recapitulate normal functional organ or tissue architecture. Key processes occurring during both *in vitro* and *in vivo* phases are: 1) cell adhesion, proliferation, sorting and differentiation, 2) ECM production and organization, 3) scaffold degradation and 4) remodeling and potentially growth of the tissue.

Studies have shown that constructs composed of vascular wall or mesenchymal stem cells seeded on bioresorbable polymer sponges formed in the configuration of natural valves can be implanted into and function in the pulmonary artery of sheep for months, and that the remodeling of these TEHV recapitulate features of normal tissue development, differentiation and growth. In addition, accumulating evidence suggests that circulating progenitor cells with the potential to differentiate into valvular cells can be recruited in-vivo from the bone marrow to cardiovascular sites and biomaterials. Thus, an alternative approach to TEHV might harness the properties of endogenous cells to seed of a polymer valve configuration or decellularized valve substrate *in- vivo*.

The Challenges Ahead: Opportunities afforded by the potential of TEHV are indeed exciting, but the clinical translation of TEHV holds many challenges and unanswered questions. They include the need to 1) develop guidelines to assure safety, efficacy, and quality of tissue constructs; 2) understand mechanisms of tissue formation and remodeling, 3) define animal models, 4) develop biomarkers and tools that define and measure surrogate and true endpoints of performance to predict outcomes as early as possible; and 5) accommodate patient-to-patient heterogeneity in tissue remodeling.

Reference: Mendelson KM, Schoen FJ: Heart valve tissue engineering: Concepts, approaches, progress, and challenges. Ann Biomed Engin 2006; 34:1799.