

## James & Esther King Biomedical Research Program

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*New Investigator (3-year project)*

**Project Title:** Molecular Regulation of Heart Valve Development and Disease

**Project Summary:** Epidemiological studies have identified tobacco use as a clinical risk factor for increasing the incidence of cardiovascular disease including calcification of heart valve leaflets. Despite the clinical relevance, the fundamental mechanisms that lead to calcification of valve structures are not known. Human studies are beginning to provide evidence that developmental pathways important in valvulogenesis also contribute to adult valve disease. During development, valve precursor (VP) cells and extracellular matrix (ECM) differentiate and express markers characteristic of cartilage, tendon, and bone. Following birth, valve interstitial cells (VICs) and ECM become highly organized within the valve structures to facilitate and maintain normal valve function. Diseased or malfunctioning adult valves are associated with alterations in ECM homeostasis and VIC distribution. The regulatory pathways required for normal valve development are poorly defined, yet understanding these processes may provide important insights into mechanisms of tobacco-related valve calcification. Recent work has shown that signaling pathways common to cartilage cells also regulate VP cell differentiation of lineages that contribute to the valve leaflet. During chondrogenesis Sox9 regulates expression of cartilage genes, a regulatory pathway that appears to be conserved in cartilage-like cells during valve development. However in developing bone, Sox9 expression is reduced with increased expression of bone matrix proteins, suggesting that Sox9 function plays a pivotal role in maintaining chondrogenesis and repressing bone formation in tissues that must remain cartilaginous. Calcified valves display alterations in Sox9 expression and ectopically express bone matrix proteins, suggesting that aberrations in Sox9 function may lead to alterations in ECM homeostasis and valve disease. The molecular mechanisms of Sox9 required for ECM homeostasis in normal embryonic and adult valves are not clear and may be important in calcified valve disease. The overall hypothesis is: Sox9 is required to maintain ECM homeostasis in normal embryonic and adult valves by directly regulating expression of cartilage-associated genes and inhibiting expression of bone-related genes, thus preventing pathological calcification. Our experiments will specifically determine if: 1) Sox9 is necessary and sufficient for promoting expression of cartilage-associated genes and inhibiting expression of bone-related genes in murine VP cells during development and VICs during normal adult valve maintenance; 2) Sox9 directly binds regulatory elements of cartilage-associated genes in tissue from developing endocardial cushions that contain VP cells, normal adult valve leaflets, and calcified leaflets in vivo; 3) Sox9 maintains ECM homeostasis and prevents pathological calcification of heart valve tissue in vivo. These studies will examine the molecular mechanisms of Sox9 for ECM homeostasis during valve development, maintenance, and disease using in vitro and in vivo systems of pathological valve calcification. Using these systems we aim to test the proposed hypothesis and significantly improve current diagnostic and therapeutic applications of valve calcification associated with tobacco use.