NIH Award from the National Heart, Lung, and Blood Institute

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- **Project:** Role of Lrp5/Beta-Catenin in Aortic Valve Calcification
- **Start Date:** July 15, 2009
- **Total Award Amount:** $251,573

**How the results of this project will benefit society:**
Aortic valve stenosis is a common consequence of the traditional risk factors for vascular atherosclerosis including: hypertension, hypercholesterolemia, smoking, increased BMI, aging and diabetes. Once thought to be caused by a passive process involving calcium attaching to the valve leaflet, there is growing evidence to support that hypercholesterolemia can induce the valve myofibroblast cell to differentiate to an osteoblast-like phenotype. The ability to treat or slow the progression of aortic valve calcification (AVC) represents an unmet clinical need.

**The problem the project is trying to solve:**
Understanding of AVC initiation and progression is required for future therapies for this disease. A growing number of laboratories are demonstrating that osteogenic gene programs in calcifying cardiovascular tissue involve complex signaling pathways similar to bone biology. We hypothesize that lipids regulate the Lrp5/Wnt/b-catenin cascade in aortic valve myofibroblast cells to express the osteogenic gene program. Statin agents reverse this differentiation pathway via inhibition of Lrp5 in the myofibroblast cell. We have shown that statins inhibit calcification and Cbfal gene expression in the aortic valve.

**How this project will work:**
In this proposal we will study the role of low density lipoprotein receptor-related protein (5 Lrp5) receptor in the lipid regulation of the Lrp5/beta catenin-Cbfal signaling in AVC. Aim 1 will test whether activation of Lrp5 signaling by lipids is sufficient to induce bone formation in aortic valve myofibroblasts. Aim 2 will investigate whether statins and other candidate inhibitors of Lrp5 signaling can inhibit the osteoblastogenesis pathway in these cells. Aim 3 will define the role of Lrp5/beta-catenin in the development of aortic valve calcification and osteoporosis by testing experimental hypercholesterolemia on the LRP5-null, LDLR-null and the double knock-out for the LDLR/Lrp5 receptors mice. Aim 4 will use the TOPGAL+ and the LRPS-/- TOPGAL + reporter mice (LacZ transgene under control of Wnt-responsive TCF/LEF element) to determine if lipids can activate diet-induced Cbfal-Wnt expression and induce bone formation in aortic valve myofibroblasts and inhibit bone formation in the osteoblasts from the bones. Our long term goal is to understand the role of Lrp5/beta-catenin in aortic valve calcification and how this information may be used to develop more effective therapies. The objectives of this proposal are to determine if the Lrp5 receptor is critical in activation of mineralization in aortic valve calcification.

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