Research Profile: Tremendous unmet needs exist in musculoskeletal medicine. Osteoporosis and osteoarthritis are recognized as common and clinically important, but other serious skeletal disorders also afflict our society. In the setting of type 2 diabetes mellitus (T2DM), lower-extremity musculoskeletal disease is prevalent, costly, and exceedingly difficult to manage, with fracture, arthropathy, ischemia, ulcer, infection, and amputation commonly confronting patients and clinicians. Aortofemoral medial artery calcification is a strong predictor of risk for lower extremity amputation in patients with T2DM. While not occluding the lumen, mural elastinolysis and medial calcification compromise arterial elasticity -- a material property necessary for Windkessel physiology that ensures normal tissue perfusion throughout the cardiac cycle. During aortic calcification, the Msx-Wnt signaling cascade that controls orthotopic craniofacial bone formation is activated ectopically in the aortic valve and vessel wall. Diabetes and dyslipidemia induce expression of Msx2 in arterial myofibroblasts, upregulate aortic Wnt3, Wnt4, Wnt7, and Wnt10a gene expression, and activate pro-calcific canonical Wnt signaling in the valve and tunica media. By studying Msx2 actions, we have identified that paracrine Wnt/Dkk signals control arterial calcification and fibrosis in T2DM by regulating the osteogenic lineage allocation of vascular mesenchymal progenitors. Prosclerotic inflammatory Wnt signals initiated by TNF-alpha and osteopontin -- but inhibited by vascular LRP6 and PTH1R -- modulate the sustained activation of this arterial injury response. Intracellular protein arginine methylation / demethylation has recently emerged as a novel feature of the Wnt/LRP6 regulatory relay. We study how strategies that differentially modulate skeletal vs. arterial Wnt signaling preserve bone homeostasis and cardiovascular health in chronic disorders such as diabetes, uremia, and cystic fibrosis.

Techniques: Murine and human molecular genetics; arterial and skeletal physiology including mineralization, structure and mechanical stiffness; primary cell culture and cell respirometry; site-directed mutagenesis; protein biochemistry including post-translational modification and protein-protein interactions by western blot and mass spectrometry; RNA metabolism and quantitative gene expression in cells, tissues, and plasma exosomes; transcription assays including luminometry and chromatin immunoprecipitation; ChIP-Seq and RNA-Seq; histology with immunohistochemistry and immunofluorescence microscopy.

Selected Recent Publications:

