

James & Esther King Biomedical Research Program

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*2007 Program
Team Science Project (2-year project)*

Project Title: Cellular Therapeutics and Mechanisms of Vascular Dysfunction in Heart and Kidney Disease

Project Summary: This grant focuses on the mechanisms of blood vessel growth, injury, and repair that underlie coronary artery disease, ischemic heart disease, and chronic kidney disease. The overriding theme is that defects in blood vessel repair accumulate during aging, and this results in the atherosclerotic lesions (hardening of the arteries) that cause both myocardial and renal ischemia (lack of blood supply) and ultimately organ failure. The process of atherosclerosis is accelerated by the multiple risk factors that are associated with these diseases including tobacco use. The combined goals of this research program are both mechanistic (cause of disease) and therapeutic (treatment); we will determine how nicotine promotes the growth of plaque on the vessel walls and whether this can be “cured” by introducing a subset of specialized stem cells derived from the bone marrow. In a combined clinical and basic study, we will attempt to determine whether aging and other cardiovascular disease risk factors cause defects in a specialized fraction of human bone marrow-derived stem cells that are essential for blood vessel growth and repair. Two of our investigators recently made the novel discoveries that human blood vessel smooth muscle cells and kidney mesangial cells both bind nicotine directly (mesangial cells are specialized smooth muscle cells that surround the vessel walls within the kidney). They made the parallel observations that nicotine accelerates the process of atherosclerosis in these organs, thereby identifying nicotine as an independent risk factor for vascular disease. These investigators will now attempt to determine how nicotine adversely modulates the function of their target cells within the vessel walls. Stem cells are the tools of regenerative medicine, and there is much excitement that they can be used to treat coronary artery disease. Investigators from this program recently made two discoveries that could change the direction of this field. In the first, we identified an abundant fraction of cells within the bone marrow of young animals that may be able to slow or prevent atherosclerosis. In the second, we identified defective growth factor gene expression in a subset of bone marrow-derived stem cells from aged animals. If the same defects are present in humans, it may be possible to correct them and significantly improve stem cell therapy for patients after heart attack. Defective cellular functions within blood vessel walls and the role of stem cells both as causal and curative agents is the common thread that unites and synergizes this program. Results from these studies will give us new insights into how to prevent and treat cardiovascular and kidney disease, the major complications of tobacco use.