

Abstract: Stem Cells and Cardiovascular Repair

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This Administrative Supplement is aimed at determining the effect of smoke exposure on the engraftment of human embryonic stem cell-derived cardiomyocytes (hES-CMs) utilized in the therapeutic repair of myocardial infarction. Specifically, we will compare the effect on functional engraftment in smoke-exposed to non-smoke exposed animals. Furthermore, we will compare the effect of smoke generated by traditional cigarettes to that generated by E-cigarettes. This confounding variable is particularly relevant to our mechanistic studies, given that 40-70% of patients currently enrolled in stem cell trials aimed at cardiac repair have a history of smoking.

Over the course of these experiments, we will address 3 aspects critical to the functional engraftment of hES-CMs, all of which will be performed concurrently with those experiments currently underway as part of our original SCCaR P01. Aim 1 (Murry) is designed to determine the effect of smoke, and the individual constituents of smoke, upon the basic properties of hES-CMs in vitro (i.e., differentiation, migration, proliferation, Ca²⁺ handling, EC coupling, etc.). Aim 2 (Mahoney) is designed to determine the effect of smoke exposure on the vascularization of myocardially-implanted grafts in the mouse model of myocardial infarction. Finally, Aim 3 (Laflamme) is designed to determine the effect of smoke exposure on the electromechanical integration of myocardially-implanted grafts in the guinea pig model of myocardial infarction.

Furthermore, these experiments will be designed and executed in consultation with the Smoking/Toxicology Advisory committee, comprised of Drs. David Eaton and Terrance Kavanagh (UW Center for Ecogenetics and Environmental Health) and Dr. William Parks (Director, UW Center for Lung Biology). This advisory committee will provide the institutional support to initiate these studies, and during the early phase of this grant, we will collaborate with Dr. Parks utilize the same mice, exposed to smoke at Washington University, to study the effects of smoke from traditional and E-cigarettes on the innate cardiac vascular organization, in the absence of myocardial injury.