**A NANOMEDICAL APPROACH TO THE RESTORATION OF DYSFUNCTIONAL ENDOTHELIUM AND THE FUNCTION OF THE CARDIOVASCULAR SYSTEM**

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*Background:* A dysfunctional endothelium is a common denominator in aging and several cardiovascular diseases: hypertension, diabetes, salt-induced hypertension and atherosclerosis. Dysfunctional endothelium is characterized by diminished concentrations of cytoprotective nitric oxide (NO) and an overproduction of cytotoxic peroxynitrite (ONOO-) and superoxide (O2-).

*Methods & Results*: A nanomedical approach was utilized to directly measure with nanosensors (diameter of 150-250 nm) the near real time (1microsecond) changes of NO, O2- and ONOO- concentrations released from endothelial cells. The concentration ratio of [NO] to [ONOO-] and [O2-] was used to quantify the level of endothelial dysfunction. The studies presented here elucidate different treatments of dysfunctional endothelium which may lead to the correction/restoration of endothelial function and to hinder the rate of progression of aging and /or cardiovascular disease. [NO]/[ONOO-] ratio in normal endothelium is about 3-5 and the ratio uf [NO]/[ONOO-+[O2-] is in the range of about 1.8-2.7. In cellular and/or animal models of hypertension, diabetes or aging, the [NO]/[ONOO-]+[O2-] ratio is usually below 0.70 and can decrease dramatically to a level of 0.1 in advanced stages of disease.

There are two major sources that contribute to the generation of O2-in endothelium, uncoupled eNOS and NAD(P)H. NO is an efficient scavenger of O2- to produce ONOO-. Uncoupled eNOS accounts for about 60% of O2-, while about 40% is produced by NAD(P)H. In normal endothelium, the major source of O2- production comes from NAD(P)H, while production from eNOS is negligible. Several different treatments were used to elucidate the restoration/improvement of endothelial function: scavenging of O2- (PEG-SOD), scavenging of ONOO- (Mn(III) TM PyP), increase of eNOS coupling and the efficiency of NO production (NAD(P)H, L-arginine, sepiapterin and statins). Using these various treatments separately or in combination can restore dysfunctional endothelium by 70-95% in cellular and animal models of hypertension, diabetes and aging.