Sepsis, a life-threatening systemic inflammatory disorder, has an incidence of between 130 to 430 per 100,000 population in Western countries and is associated with fatality rates as high as 20-40%. The outcome of sepsis in elderly patients is substantially worse than in younger patients. Endothelial dysfunction importantly contributes to pathophysiology of sepsis and recent studies by the applicant and other groups provide key evidence that pro-inflammatory stimuli and oxidative stressors induce a significantly more severe degree of endothelial dysfunction in blood vessels of aged rats and mice, when compared to the responses in young animals.

Despite the evidence that aging sensitizes the vasculature to the deleterious effects of pro-inflammatory factors and oxidants, and despite the fact that circulatory shock primarily affects the aging population, and despite the fact that the age of the population continues to increase in developed countries, surprisingly, there are currently no studies specifically focusing on the mechanisms underlying the sepsis-associated impairment of endothelial function in aging animals.

The central hypotheses of the present application are that (1) accelerated endothelial dysfunction is a key contributor to multiple organ failure and mortality in aging animals during sepsis and (2) in aging blood vessels, unique cellular and molecular mechanisms operate that render them extremely vulnerable to the oxidative stress-associated endothelial dysfunction during sepsis. Based on novel preliminary data, we will test the hypothesize that impaired activation of Nrf2 (a master regulatory factor of the antioxidant response) is involved in the development of endothelial dysfunction in aging blood vessels during sepsis and this is linked to nuclear enzyme PARP, acceleration of telomere loss and or/and age-associated down-regulation of circulating IGF1 levels. Furthermore based on proteomic and metabolomic approach we will identify unique pathophysiological patterns and will yield potentially targetable novel pathways that are selectively perturbed in the aged vasculature in response to sepsis.

This project should shed light on the pharmacotherapeutic mechansisms of age-associated worsening of endothelial dysfunction in sepsis. This topic represent an important challenge in medicine given the fact that as yet there are no effective pharmacological approaches for the therapy of circulatory shock and multiorgan failure of sepsis.