The signaling molecule nitric oxide (NO), produced in endothelium by endothelial nitric oxide synthase (eNOS), plays a pivotal role in the maintenance of homeostasis in the blood vessel wall. Impaired activity of eNOS and the loss of NO bioavailability are associated with endothelial cell dysfunction that is itself an independent risk factor for cardiovascular diseases. Importantly, hypoxia and ischemia lower endothelial eNOS expression, leading to loss of NO bioavailability. In these cases, a major contributing factor to downregulation of eNOS expression appears to be a reduction in the stability of the mature eNOS transcript.

Our working hypothesis is that during hypoxia specific non-coding RNA molecules microRNAs (miRNAs) reduce endothelial eNOS levels and consequently decrease the bioavailability of NO.

Hence the main overreaching goal of this application is to determine whether eNOS mRNA and consequently endothelial bioavailability of NO can be actively stabilized/modulated in order to protect it from the inhibitory effects of the miRNAs.

The role of miRNAs in governing endothelial bioavailability of NO is not well understood, and has potentially far-reaching implications in many types of cardiovascular pathologies. Given that miRNAs specific target protectors can potentially be used in future therapeutic approaches the studies proposed herein.
Consequently in this study we will:

Aim 1. test the hypothesis that miRNAs control NO bioavailability during hypoxia in human endothelium in a tissue-specific manner.

Aim 2. test the hypothesis that eNOS/sONE specific miRNA analogs can be used to modulate bioavailability of NO.