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Project Title: Mitochondrial reactive oxygen species signalling and cardiovascular disease mechanisms

Angiotensin II (Ang II) is an important mediator of cardiovascular (patho)physiology in man, and amongst a plethora of effects, promotes vascular smooth muscle cell (VSMC) growth and apoptosis.

Our recent data¹ showed that Ang II also induces accelerated replicative senescence in human primary VSMC via telomere attrition due to enhanced reactive oxygen species (ROS) production and DNA damage. Higher levels of Ang II preferentially induced apoptosis. Telomere attrition, apoptosis and senescence of vascular cells at sites of atheroma in man and experimental animals strongly implicate biological ageing in the development of cardiovascular disease (CVD). Importantly, our investigations also showed that Ang II mediated stress-induced premature senescence, independent of telomere loss but dependent on ROS production.¹ Preliminary data suggested that inhibition of mitochondrial oxidant production completely prevented the pro-ageing effects of Ang II; links between telomere biology and mitochondria function with relevance to cardiovascular ageing have now been described.²

The current project builds upon these findings and aims to provide proof of principle that targeting mitochondrial ROS ameliorates the effects of a mediator that is strongly associated with risk of CVD and cardiovascular ageing. In man, elucidation of mechanisms for the effects of Ang II, independent of effects on blood pressure, may suggest novel therapies with more specific and potent effects, for example antioxidants targeted to mitochondria.³

The project would be suitable for a hard-working, enthusiastic and self-motivated individual with a strong interest in cellular and molecular mechanisms of cardiovascular disease.

Selected References

1. Herbert KE, Mistry Y, Hastings R, Poolman T, Niklason L, Williams B. Angiotensin II-mediated oxidative DNA damage accelerates cellular senescence in cultured human vascular smooth muscle cells via telomere-dependent and independent pathways. *Circ Res*. 2008; 102:201-8.
2. Sahin E, *et al*. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature*. 2011; 470:359-65.
3. Murphy MP. Targeting lipophilic cations to mitochondria. *Biochim Biophys Acta*. 2008;1777:1028-31.