Microparticles as biomarkers of early changes leading to cardiovascular disease in chronic kidney disease

Application deadline: Applications accepted all year round

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Summary

Cardiovascular disease is the principal cause of death in chronic kidney disease (CKD). It has been proposed that CKD leads to activation and apoptosis of vascular endothelial cells (VECs), blood platelets and vascular smooth muscle cells (VSMCs) culminating in generation of cell-membrane-derived microparticles (MPs) which are both markers and potential causes of cardiovascular disease. We have shown that circulating MPs in patients with CKD exert potent pro-thrombotic effects (thus contributing to cardiovascular risk) and that hyperphosphataemia (elevated plasma inorganic phosphate (Pi)) which occurs in advanced CKD, can be a potent signal triggering cell growth/activation and apoptosis.

The hypothesis is that hyperphosphataemia elevates intracellular Pi concentration in VECs, platelets and VSMCs which then serves as a signal triggering MP formation.

The project involves carefully supervised training in a wide range of molecular, cellular and in vivo research methods, specifically:

1) Using molecular methods to manipulate Pi transporter expression and intracellular Pi in human VECs, and arterial VSMCs, and determining the resulting protein phosphorylation signals downstream from Pi which result in MP generation

2) Varying plasma [Pi] (by dietary Pi manipulation) in vivo in a rat model of CKD to determine the resulting effects on apoptosis of arterial cells, circulating MPs, and thrombin generation

3) Performing similar plasma MP measurements in healthy subjects and CKD patients, and correlating these with plasma Pi and variables predicting cardiovascular risk and outcome.