Oxidation of uric acid in inflammatory diseases

Uric acid is a mystifying metabolite. Evolution has selected it to accumulate in the plasma of humans but whether it has essential physiological functions remains unknown. At physiological pH uric acid exists predominantly as its conjugate base, urate. Its apparent protective effects in Parkinson’s disease suggest that urate may be an important antioxidant in the brain. Yet high concentrations of urate in blood are associated with several inflammatory pathologies. The most commonly known association is with gout, where urate precipitates to form crystals that activate the immune system, provoking intense pain and swelling in affected joints. There are also intriguing links with high urate levels and adverse outcomes in a variety of diseases including cardiovascular disease and chronic kidney disease.

Our hypothesis is that when urate is oxidized it gives rise to toxic metabolites that exacerbate inflammation. In this project we will study the reactivity of one of these metabolites- urate hydroperoxide. This reactive oxygen species is formed when urate is oxidized in the presence of superoxide. We aim to show how fast urate hydroperoxide reacts with small antioxidants such as ascorbate and glutathione as well as how readily it reacts with enzymes such as peroxiredoxins and GAPDH. We also want to identify the products of these reactions. Knowledge gained from this project will be essential for understanding why high concentrations of urate are detrimental to health.

Indicate preferred student expertise: This project will suit an enthusiastic student with a good background in chemistry and biochemistry.