2014/2015 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on **4 July** 2014

Supervisor Information (First named supervisor will be the contact):	
Supervisor's Name(s): Professor Tony Kettle	
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Research Category (Choose one category only – to be used for judging the students' presentations):		
Clinical	**Laboratory ✓**	**Community**

Project Title (20 words MAXIMUM):

Reactions of urate hydroperoxide with biological targets

Project Description:

Background:

Uric acid is the final product of purine metabolism. It exists as urate at physiological pH. Urate has no clearly defined biochemical function but has been proposed to function as an antioxidant. High concentrations of urate in plasma (hyperuricemia) are associated with gout, cardiovascular disease, diabetes, and metabolic syndrome. We have recently found that when urate is oxidized in the presence of superoxide, it forms urate hydroperoxide. This species is expected to react with numerous biological molecules and is likely to be cytotoxic. It will be formed during inflammation when neutrophils are stimulated to produce superoxide. Consequently, urate hydroperoxide may contribute to the complications of hyperuricemia that are associated with inflammatory diseases.

Hypothesis:

Urate hydroperoxide reacts rapidly with biological targets and forms adducts with proteins.

Aims:

1. To chemically synthesize urate hydroperoxide and determine its structure by mass spectrometry.
2. To determine how fast urate hydroperoxide reacts with biological targets such as the amino acids methionine and cysteine as well as the antioxidant ascorbic acid.
3. To determine whether urate hydroperoxide forms adducts with amine and thiol groups on peptides.

Methods:

Urate hydroperoxide will be synthesized by a published method in which urate is reacted with oxygen and riboflavin in the presence of a source of UV light. It will then be analysed by liquid chromatography with mass spectrometry to identify its mass and fragmentation pattern. These data should provide sufficient information to elucidate its chemical structure. Its reactivity with biological molecules will be determined by measuring how fast it is lost in these reactions. Its concentrations will be measured over time using the ability of hydroperoxides to oxidize a complex of ferrous iron and xylenol orange to a purple complex. Urate hydroperoxide will be reacted with peptides containing amine or cysteine residues and the products identified by mass spectrometry. All these methods are currently used in the Centre for Free Radical Research. The mass spectrometry work will be done under the supervision of an experienced mass spectrometrist.

Student Experience: The student will be introduced to physical aspects of chemistry, such as structural elucidation and reaction kinetics, that are important in the understanding of toxicology. She will also have the unique experience of using mass spectrometry; a method that is usually available only to post-graduate students. It is expected that the data generated in this project will be published in a peer reviewed journal. The student would be an author on the paper that arises from this work.