2015/2016 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on **3 July 2015**

Supervisor Information (First named supervisor will be the contact):	
Supervisor's Name and Title(s): Prof Tony Kettle & Dr Louisa Forbes	
Department: Pathology	Institution: UOC or CDHB
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Mailing Address:	

Research Category (Choose one category only – to be used for judging the students' presentations):		
Clinical	**Laboratory ✔**	**Community**

Project Title (20 words MAXIMUM):

Inactivation of enzymes by urate hydroperoxide and protection by ascorbic acid

Project Description:

Introduction:

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. We have shown that it inactivates thiol dependent enzymes but have yet to establish the mechanism of inactivation. These enzymes included protein tyrosine phosphatases that have important roles in cell signalling. The damaging reactions of urate hydroperoxide are likely to be in competition with its reduction by ascorbic acid.

Hypothesis:

Ascorbic acid prevents urate hydroperoxide from reacting with critical cysteine residues on enzymes and forming irreversible adducts.

Aims:

1. To determine how fast urate hydroperoxide reacts with ascorbic acid.
2. To determine how urate hydroperoxide inactivates protein tyrosine phosphatases.
3. To determine whether ascorbic acid prevents inactivation of enzymes by urate hydroperoxide.
4. To determine whether urate hydroperoxide forms adducts with thiol groups on peptides and proteins.

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 or using the enzymes xanthine oxidase and lactoperoxidase. Its reactivity with biological molecules will be determined by measuring how fast it is lost in these reactions and by loss in enzyme activity. Urate hydroperoxide will be reacted with peptides containing 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: This project has been designed for Melanie Hamzah who is a current B.Biomed.Sci (Hons) student. The studentship will give her the opportunity to complete a study on urate hydroperoxide and write an initial draft of a publication.

Student Prerequisites (eg. Medical Student) if applicable:
None