

Monday, February 23rd, 2015

LSC 3 - Life Sciences Centre

2350 Health Sciences Mall

12-1pm



## Dr. Robert Pike

*Director, La Trobe Institute for Molecular Science*

*Head of School – Molecular Sciences*

**“Polyanionic cofactors of the serpin, C1-inhibitor, for the treatment of inflammatory diseases”**

Polyanions, such as heparin, have long been used to modulate human hemostatic mechanisms. In order to achieve these effects, they act as cofactors of human serpins, such as antithrombin. Heparin has also been found to have cofactor activity for the serpin, C1-inhibitor, which acts to regulate proteases of the complement, kallikrein-kinin and coagulation systems. Due to these effects and other intrinsic features of its structure, C1-inhibitor is a strongly anti-inflammatory molecule. It is approved for use in treating hereditary angioedema in humans: this is a disease caused by a lack of control of the human kallikrein-kinin system due to a deficiency in the serpin.

There is considerable potential in the application of C1-inhibitor for treatment of inflammatory conditions. The complement system is most likely involved in the pathogenesis of a number of inflammatory diseases, such as arthritis and ischemia-reperfusion injury. We have been investigating the mechanism of the cofactor activities of a number of polyanions involved in controlling the association between C1-inhibitor and target proteases in the complement system. Recent data indicates that pathway selective inhibition of such proteases can be achieved using different polyanions in conjunction with C1-inhibitor. These studies open new avenues for the design of cofactors that allow selective targeting and upregulation of an endogenous inhibitor of pro-inflammatory pathways in humans.

Monday, February 23rd, 2015

LSC 3 - Life Sciences Centre

2350 Health Sciences Mall

**12-1pm**



## Dr. Lakshmi Wijeyewickrema

*Postdoctoral Fellow, La Trobe University*

### **“Novel complement inhibitors of haematophagous arthropods”**

The complement system is vital to host immune defences, but is also involved in inflammatory diseases, e.g. arthritis and ischemia-reperfusion injury following heart attack. There is a strong need for therapeutic molecules that modulate complement in order to achieve anti-inflammatory outcomes in these disease states. We have been able to show that enzymes in the different pathways of complement activation have a number of sites crucial to their function in addition to their active sites, so called exosites. We propose that these exosites are key points for the design of molecules that are able to specifically interfere with the functions of these enzymes and thus have immunomodulatory effects.

The saliva of blood-feeding organisms has potent effects on host haemostatic and immune systems. Locally, the salivary molecules alter host responses to allow the vector to feed. One method that such molecules use to counteract host-derived inflammation is to impair complement.

We have investigated the complement modulating activity of a number of molecules derived from the medicinal leech and arthropods. An inhibitor from the leech has been found to have strong inhibitory effects on complement enzymes by targeting the exosites of these enzymes. Such molecules are likely to provide novel scaffolds for the design of therapeutic moieties that could be used to modulate the complement system in inflammatory diseases.