

Wednesday, July 23rd, 2014

LSC 3 - Life Sciences Centre

2350 Health Sciences Mall

12-12:30pm



## Dr. Antoine Dufour

*Postdoctoral Research Fellow*

*Department of Oral Biological & Medical Sciences*

*Centre for Blood Research, UBC*

### **“Macrophage Matrix Metalloproteinase-12 Dampens Inflammation and Neutrophil Recruitment: Pleiotropic Protective Roles Revealed by Terminomics”**

Resolution of inflammation prevents pathological tissue destruction and restores tissue homeostasis. We used proteomics to globally analyze the role of the macrophage specific matrix metalloproteinase-12 (MMP12) in murine models of peritonitis and arthritis. Applying a proteomic substrate discovery approach, TAILS, we found that MMP12 executes several anti-inflammatory roles through cleavage of multiple substrates in vivo. The activated partial thromboplastin time was significantly prolonged in *Mmp12*<sup>-/-</sup> plasma due to MMP12 inactivation of antithrombin III and activating prothrombin. MMP12 inactivated complement C3, which reduced complement activation, and inactivated the chemoattractant anaphylatoxins C3a and C5a, whereas iC3b and C3b cleavage increased phagocytosis. Loss of these anti-inflammatory activities in collagen-induced arthritis in *Mmp12*<sup>-/-</sup> mice led to unresolved synovitis and articular inflammation. Deep articular cartilage loss was associated with massive neutrophil infiltration and abnormal neutrophil extracellular traps (NETs) of DNA. The NETs were rich in fibrin and extracellular actin, which TAILS identified as MMP12 substrates. Thus, macrophage MMP12 in arthritis has protective roles in countering neutrophil infiltration, clearing NETs and dampening inflammatory pathways so preparing for the resolution of inflammation.