Antoine Dufour

My recent appointment in August 2017 within the department of Physiology & Pharmacology at UCalgary has allowed me to explore, using proteomics, the biological mechanisms underlying proteases processing of their substrates during Ca^{2+} stimulation in macrophages playing pathogenic roles in autoimmune and chronic inflammatory diseases. My lab is interested in understanding the proteolytic regulation of leukocytes during immune and inflammatory responses[1]. The role of the neutrophil specific MT6-MMP was demonstrated to cleave various substrates using quantitative proteomics approaches. In chronic inflammation, MMP-12 stops neutrophil influx, terminates complement activation and clears neutrophil extra-cellular traps to prepare for the resolution of inflammation. Our lab has investigated the role of MMP12 in various clinical samples including chronic obstructive pulmonary disease samples (sputum) and found, using quantitative proteomics, a novel role of MMP12 to activate the signaling pathways of lung epithelial cells by cutting a cell surface receptor[2]. In autoimmunity, MMP12 was shown to cleave IFN-gamma to attenuate the classical activation of macrophages and terminate downstream signaling of Janus Kinase (JAK)-signal transducer and activator of transcription 1 (STAT1) phosphorylation[3].

My lab is investigating the role of virus proteases and is aiming to identify the substrates they cleave during infection. Our team showed that MMP-12, an extracellular macrophage protease, is translocated to the nucleus, to drive transcription. This initiates the secretion of IFN-α and in later infection time, MMP-12 cleaves IFN-α terminating its long-term effects in a negative-feedback loop. Another example of the importance of proteases in virology was demonstrated by identifying the novel substrates of the poliovirus and coxsackievirus B3 3C proteinases in facilitating viral infection[4].

My lab has recently identified Proteoglycan 4 (PRG4) as a novel substrate of mast cell tryptase; PRG4 is cleaved within the cartilage in rheumatoid arthritis leading to a decreased in lubrication and activation of immune cell signaling pathways[5]. In Sjogren's syndrome patients, PRG4 processing was found to be increased in the inflamed joints but also in the eyes of patients leading to pathogenic dry eyes syndrome.

Research website: www.dufourlab.com

Selected Publications:

1- **Dufour, A.** and Overall, C. M. Missing the target: matrix metalloproteinase antitargets in inflammation and cancer. *Trends Pharmacological Sciences* **34,** 233–242 (2013).

2- Mallia-Milanes B, **Dufour, A**. *et al.* TAILS proteomics reveals dynamic changes in airway proteolysis controlling protease activity and innate immunity during COPD exacerbations. *American Journal of Physiology,* Accepted (2018).

3- **Dufour, A**. *et al.* C-terminal truncation of IFN-γ inhibits proinflammatory macrophage responses and is deficient in autoimmune disease. *Nature Communications* **9,** 2416 (2018).

4- Jagdeo, J. M., **Dufour, A,** *et al.* N-Terminomics TAILS Identifies Host Cell Substrates of Poliovirus and Coxsackievirus B3 3C Proteinases That Modulate Virus Infection. *Journal of Virology* **92,** e02211–17 (2018).

5- Das N, Schimdt T, Krawetz R and **Dufour, A**. Proteoglycan 4: From mere lubricant to regulator of tissue homeostasis and inflammation. *BioEssays,* Accepted (2018).