Key players in insulin resistance and diabetes

The Marette laboratory is looking for highly motivated PhD students to join the group. The main interests of the laboratory are the multiple complex mechanisms affecting insulin sensitivity at the level of the liver, muscle, adipose tissue and the intestine. The overarching goal of our research it to identify key mediators of insulin resistance in pro-inflammatory settings such as obesity, diabetes and cardiovascular diseases, as well as the development of novel medical and nutritional approaches to alleviate these conditions. The studies in the Marette laboratory use molecular biology and system biology approaches in cell lines, isolated tissues as well as comprehensive phenotyping studies in animal models.

Following is a list of the current projects:

1. The role of nitric oxide (NO) in insulin resistance and inflammation: NO is a radical gas, which is produced naturally by a family of enzymes (NOS) including the inducible isoform (iNOS) that has been shown to play a key role in the defense against bacterial and viral infection. Our laboratory was the first to demonstrate the implication of iNOS in insulin resistance in the context of obesity (Perreault and Marette., Nature Medicine 2001). The objective of this project is to determine the contribution of iNOS to the development of insulin resistance in insulin target tissues such as liver, muscle, adipose tissue and the intestine.
2. Implication of the mTORC1/S6K1 signaling pathway in insulin resistance: Insulin signaling is tightly controlled. Binding of insulin to its receptor on the cell surface leads to a cascade of reactions including the negative feedback inhibition of its own signaling cascade via the mTORC1/S6K1 pathway to terminate insulin's action. Interestingly, this signalling pathway is highly activated in the presence of excess nutrient supply and obesity leading to insulin resistance. The goal of this project is to understand how different inhibitors of the mTORC1/S6K1 pathway could ameliorate insulin resistance in the context of nutrient excess and obesity.
3. Role of the phosphatase Shp1 in the development of insulin resistance: Insulin signaling is regulated by positive phosphorylation of key molecular targets but also by inactivation of these targets by dephosphorylations. Recently, we have identified the phosphatase Shp1 as a new inhibitor of insulin action (Dubois et al., Nature Medicine 2006). Current projects are ongoing in the Marette laboratory to clarify the precise role of Shp1 in insulin sensitivity and to determine the role of recently identified new interacting partners of the phosphatase in the control of metabolism and/or cellular growth and differentiation.
4. Effects of inflammatory resolution mediators derived from omega-3 fatty acids on metabolic syndrome: We know that the consumption of omega-3 fatty acids has beneficial health effects. Nevertheless, the mechanisms implicated in these health effects are still ill defined. We have recently shown that the omega-3 derived metabolite protectin DX (PDX) is a key player in the benefits observed by this lipid of marine origin on insulin sensitivity implicating the production of IL-6 by the muscle (White et al., Nature Medicine 2014). The goal of this ongoing research project is to study the mechanism of action and the therapeutic potential of this powerful molecule.
5. Role of intestinal microbiota in the development of obesity and associated disorders: Recent studies have shown that the gut microbiota can be considered as a *new organ* in the control of energy metabolism. The Marette laboratory proposes several studies to understand how these gut bacteria affect body weight, hepatic steatosis, insulin sensitivity and inflammation. Furthermore,

nutritional approaches are used to study how this could modulate the gut microbiota to provide health benefits.

If you are interested in a particular project, do not hesitate to contact Dr Marette and his group for more details (andre.marette@criucpq.ulaval.ca).