UNIVERSITÉ DE FRIBOURG
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# INVITATION

Conférence donnée dans le cadre de la procédure d'appel en

*Biologie - Cell or develop Biology - succ. Schwaller*


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## Tuesday 01 June 2021, à 08h15

**Présence grande auditoire de Chimie et Online via MS Teams**
Faculté des Sciences et de Médecine de l'Université de Fribourg

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## Defining the role of PI3K isoforms in metabolic and tissue homeostasis for better obesity and cancer

Class-1 phosphoinositide 3 kinases (PI3K) play a central role in the signal transduction of growthfactors and insulin, and physiological PI3K activity maintains tissue and metabolic homeostasis1. Genetic activation of PI3K signaling is a most frequent alteration in cancer, but our capacity to exploit PI3K-targeted therapy is limited by on-target adverse effects on insulin signaling driving systemic metabolic feedback loops conferring resistance to inhibitors (PI3Ki)2. Indeed, inhibition of all PI3K isoforms causes severe hyperglycemia and hyperinsulinemia, which induces PI3K activity in the tumor, causing resistance to pan PI3Ki2 . Thus, avoiding PI3Ki-induced hyperinsulinemia is key to harness the full therapeutic potential of PI3K-targeted therapies. Furthermore, several studies indicate that the insulin-PI3K pathway plays a major role in the development of obesity by inhibiting adipose tissue lipolysis and thermogenesis, indicating the possibility to treat obesity and obesityrelated diseases with a specific PI3K-targeted therapy3-8 . There are four PI3K catalytic subunits: PI3Kα; PI3Kβ; PI3Kγ; and PI3Kδ, and it was long believed that insulin signaling is mediated exclusively by the PI3Kα isoform9-12, the most frequently mutated PI3K in cancer. However, we have found that insulin signaling in the hepatocyte and in glycemic control is mediated by redundant PI3Kα and PI3Kβ activities13. This discovery indicates that it could be possible to selectively target PI3K action in tumor-promotion and in lipid metabolism without affecting glucose homeostasis by using isoform-selective PI3Ki discriminating between PI3Kα and PI3Kβ13. Furthermore, we recently reported that free fatty acids may play a major role in driving fasting hyperinsulinemia in human obese with normal glycemic control14. The role for each specific PI3K isoform in adiposity, metabolic homeostasis, and in the metabolic loops controlling insulinemia remains largely unresolved. However, we have found that PI3Kγ activity in a non-hematopoietic cell type, not yet identified, promotes adiposity in high-fat diet fed mice, in a leptin dependent manner via inhibition of PKA-driven lipolysis15; we have found that PI3Kγ activity in leukocytes promotes macrophage M1 polarization and neutrophil recruitment in the obese adipose tissue, further promoting insulin resistance16; and that systemic PI3Kγ ablation preserves β-cell mass and fasting insulin levels in the db/db mouse model of obesity-driven diabetes17.

Altogether, these results indicate that selective inhibition of PI3Kγ activity may reduce adiposity and improve glycemic control while reducing insulin levels in obese subjects. Our ongoing research focuses on the following specific aims:

1) Define the role of PI3Kγ activity within the brain-adipose axis in diet induced obesity and insulin resistance. 2) Identify the specific PI3K isoforms mediating insulin signaling and its antilipolytic action within the adipocyte and the mechanisms for such specificity. 3) Resolve the role for each PI3K isoforms in the metabolic feedback loops controlling insulin secretion. 4) Investigate the role of insulin and specific PI3K isoforms in obesity-promoted tumors, such as hepatocellular carcinoma. Our long-term goals are to achieve the necessary information to circumvent the deleterious effects of PI3K inhibition on glycemic control and insulinemia; to reposition selected isoform-specific PI3Ki under clinical development for cancer therapy to the treatment of obesity-driven type-2 diabetes by reducing excessive adiposity; and to investigate the potential of isoform-selective PI3K-targeted therapy in the treatment of obesity-promoted tumors. Because several small molecules PI3Ki with different isoform-specificity are currently under development by several pharmaceutical companies, the results from our research may be readily transferable to clinical settings.

Fribourg, le 20 avril 2021

Prof. Gregor Rainer, Doyen et
Président de la Commission d'appel