

**Thursday May 19<sup>th</sup>, 2016 - 15h00**  
Conference room AI 1153 (\*) - EPFL - Lausanne

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## Discovering Mitokine Networks in Mammalian Models

**Host:** Prof. Johan Auwerx

### Abstract:

Recent *in vivo* studies in *C. elegans* and *Drosophila* revealed that UPR<sup>mt</sup> activation by inhibition of mitochondrial electron transport chain (ETC) functions increases lifespan (Houtkooper RH et al., *Nature* 2013; Durieux J et al., *Cell* 2011) This effect of ETC inhibition on longevity is modulated by cell-autonomous and cell-non-autonomous factors, known as mitokines, which may promote metabolic homeostasis. However, extrapolation of these studies into mammalian systems is extremely difficult because generalized impairment of ETC function in mice uniformly results in progressive deterioration of organ functions and premature death. To investigate whether the role of cell-non-autonomous mitokine networks is conserved in mammalian systems, we designed a spatio-temporal approach for gene expression and secretome analysis in mice with tissue-specific UPR<sup>mt</sup> activation.

Recently, we successfully generated and demonstrated relevant mouse models of tissue-specific UPR<sup>mt</sup> activation and ETC deficiency that are reminiscent of complex human disorders, e.g., neurodegeneration (Kim et al., *Cell Metab*, 2012), Parkinson's disease, insulin resistance (Ryu et al., *PLOS Genetics*, 2013), and type 1 diabetes (Kim et al., *Diabetologia*, 2015). These models are based on tissue-specific knockout (KO) of *Crif1*, which encodes a factor required for biogenesis of ETC subunits. Loss of *Crif1* resulted in abnormal proteostasis in the mitochondrial matrix and triggered the mitochondrial unfolded protein response (UPR<sup>mt</sup>). Preliminary observations on phenotypes of tissue-specific *Crif1*-deficient mice revealed that *Crif1*-deficient cells and tissues express unique UPR<sup>mt</sup> activation e.g., adaptive transcriptomic changes and secretome responses (mitokines), which can be considered to be part of the phenomenon of "mitohormesis" (Yun J and Finkel T, *Cell Metab*, 2014). Based on these observations, we postulated that tissue-specific UPR<sup>mt</sup> and mitokine responses are critical cell-non-autonomous modifiers in disease progression, and that individual mitokines may act as disease markers and potential therapeutic targets in complex human disorders.

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