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Conference room SV 1717 - EPFL - Lausanne

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## “Defining mitochondrial protein function through systems biochemistry”

**Host:** Prof. Johan Auwerx

### **Abstract:**

Despite their position as the iconic powerhouses of cellular biology, many aspects of mitochondria remain remarkably obscure—a fact that contributes to our poor ability to address mitochondrial dysfunction therapeutically. Such dysfunction contributes to a vast array of human diseases through distinct means. For instance, aberrant mitochondrial biogenesis can fail to properly set cellular mitochondrial content; dysregulated signaling processes can fail to calibrate mitochondrial activity to changing cellular needs; and malfunctioning proteins can render core bioenergetic processes ineffectual. A major bottleneck to understanding—and ultimately addressing—these processes is that the proteins driving them are often undefined. Concurrently, the functions of hundreds of mitochondrial proteins that may fulfill these roles are not known, or at best are poorly understood. The high-level goal of my research program is to help achieve a more complete, systems-level understanding of mitochondrial biology by systematically establishing the functions of orphan mitochondrial proteins and their roles within disease-related processes. We do so by first devising multi-dimensional analyses designed to make new connections between these proteins and established pathways and processes. We then employ mechanistic and structural approaches to define the functions of select proteins at biochemical depth. This ‘systems biochemistry’ strategy is helping us address three outstanding biological questions: Which orphan mitochondrial proteins fulfill the missing steps in classic mitochondrial processes, including the biosynthesis of coenzyme Q and other aspects of respiratory chain function? What proteins assist in the orchestrated assembly of lipids, metabolites, and proteins (from two genomes) to ensure proper mitochondrial biogenesis? And, which resident signaling proteins direct the post-translational regulation of mitochondrial activities? In answering these questions, we aim to help transform the mitochondrial proteome from a component list into a metabolic circuitry of connected functions, and to elucidate the biochemical underpinnings of mitochondrial dysfunction in human disease.