Screening of pharmacological molecules to restore oxidative metabolism in rare diseases associated to mitochondrial complex I mutations

Valérie Desquiret-Dumas¹,², Naïg Gueguen¹,², Vincent Procaccio¹,², Dominique Bonneau¹,², Pascal Reynier¹,², Guy Lenaers²

¹ Department of Biochemistry and Genetics, CHU Angers / ² UMR CNRS 6015 – INSERM 1083, Mitovasc Institute, University of Angers

**Project**

Among mitochondrial diseases, Complex I (CI) deficiency is the most frequent one found in nearly thirty percent of cases. Developing a reliable and convenient therapeutic approach is considered to be a major challenge in CI-related disorders, while further researches are needed to develop and evaluate novel molecules. Our analysis of a large cohort of patients with isolated CI deficiency led us to identify a common, strong, metabolic blockade in the patients with CI assembly defect resulting in cellular metabolic reprogramming and growth defects.

In this project, we propose a cellular approach using our well-characterized fibroblast cohort of patients with a CI assembly defect to screen for molecules allowing the restoration of physiological growth, which should be associated to the reversal of the glycolytic switch and full maintenance of cell metabolism.

1 **First screening :** cell growth

2 **Ongoing :** Metabolic analyses

3 Final screening : respiration

4 Perspectives : Mechanisms?

The screening strategy proposed here is funnel-based, with three progressive selective steps that will validate the more relevant drugs targeting the metabolic blockade observed in the fibroblasts with CI assembly defect. Thus, we expect to identify molecules that specifically and efficiently target the respiratory chain and/or energetic supply pathways, in order to by-pass the metabolic blockade that play an important role in the pathophysiology of CI devastating diseases.