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

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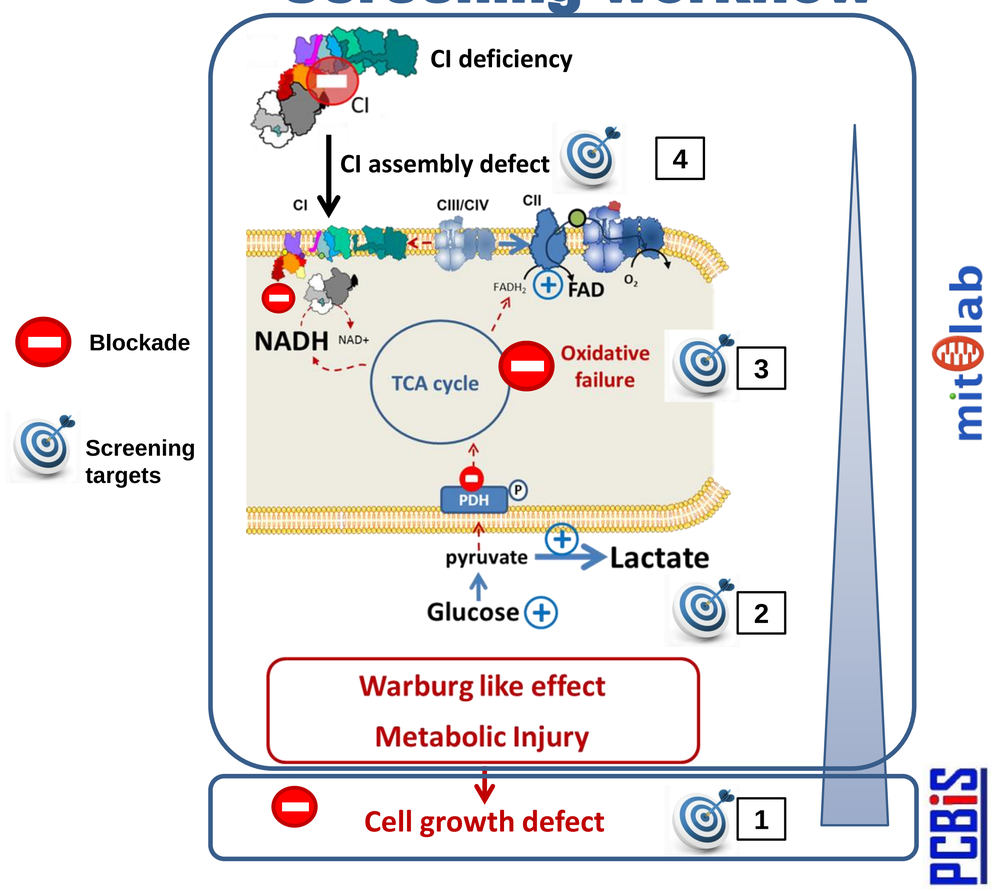
Project

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**.

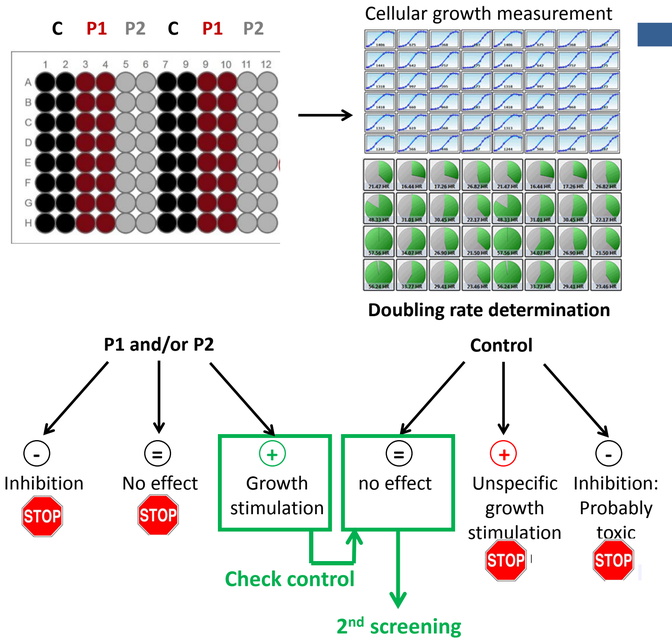
Screening workflow



1 First screening : cell growth

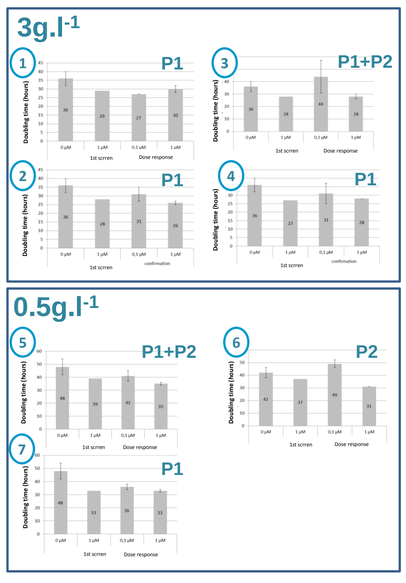
➔2 patients fibroblast cells (P1 and P2) + 1 Control (C) fibroblast cells

➔3g.l^{-1} or 0,5g.l^{-1} glucose in medium

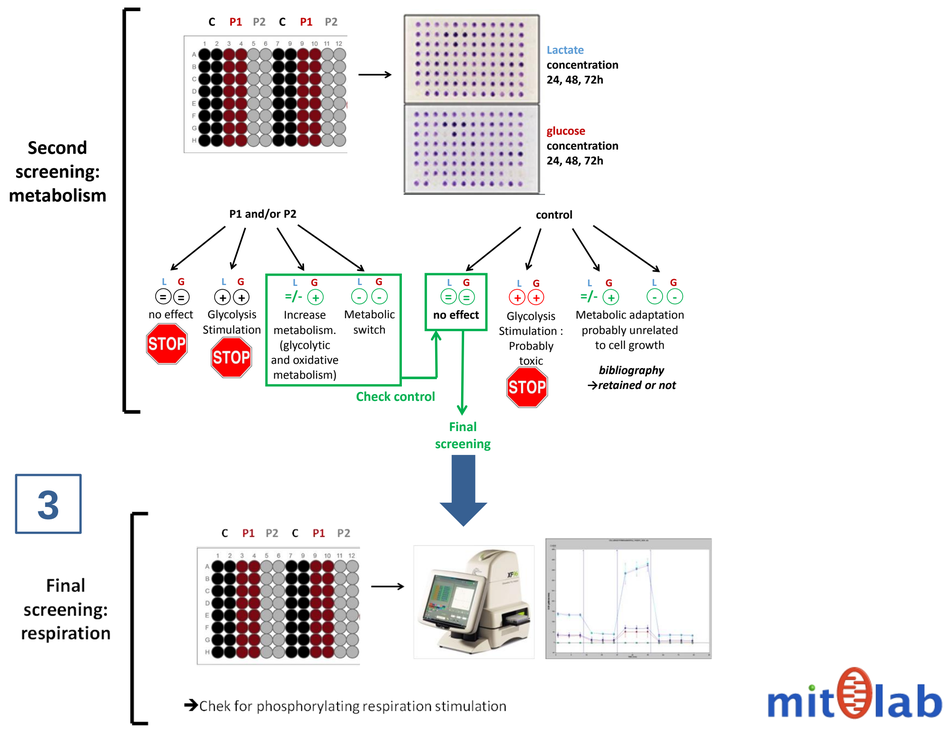


139 hits

7 hits yet confirmed by dose-response study



2 Ongoing : Metabolic analyses



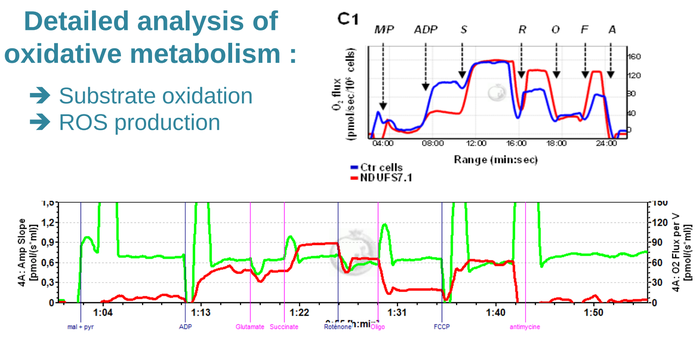
PCBiS Plateforme de Chimie Biologique Intégrative de Strasbourg, P. Villa

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.

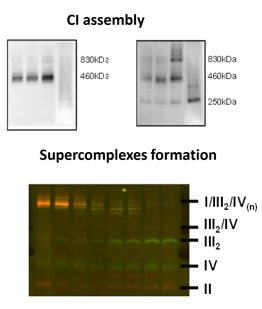
4 Perspectives : Mechanisms ?

Detailed analysis of oxidative metabolism :

➔ Substrate oxidation
➔ ROS production



Structural analyses



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