

## Therapeutic strategy against cancer escaping metabolic inhibitors

### Introduction

Metabolic alterations are common to all cancer types and represent promising targets for cancer therapy. Examples of anti-cancer therapeutic strategies aimed at tackling tumor metabolism are the treatment with metformin, the most widely used anti-Type II diabetes drug, or with inhibitors of glycolysis. However, this approach is challenged by the significant **metabolic flexibility exhibited by cancer cells**. Understanding the complexity of the molecular mechanisms driving cancer metabolic plasticity is essential to design new and more effective metabolic therapies.

### Medical Need

Differently from normal cells, cancer cells are capable to alternate between dependency on glycolysis or oxidative phosphorylation. For this reason, therapeutic strategies aimed at tackling one metabolic pathway alone are often ineffective. Thanks to their metabolic plasticity, cancer cells escape such therapies by adapting their metabolism and switching among different metabolic pathways in response to the specific stimuli. Therefore, there's a high need to design new therapeutic strategies against cancer escaping metabolic inhibitors.

### Solution

Studies coordinated by Prof. Minucci (IEO) and Prof. Foiani (IFOM) have led to the identification of a **new molecular mechanism** (mediated by a particular form of the phosphatase 2A-PP2A) located at the crosstalk between glycolysis and the oxidative phosphorylation. *In vivo* studies demonstrated that combined modulation of the glycolysis (via hypoglycemia diet or **PP2A activator molecules**) and the oxidative phosphorylation (via metformin) effectively counteracts tumor growth through the activation of the PP2A-mediated pathway. This discovery can be now exploited to develop a new therapeutic strategy against cancer escaping metabolic inhibitors.

### Advantages

- **Reduced development cost and time** through metformin repurposing;
- Combination of metformin and hypoglycemia diet currently **under clinical validation**;
- Ongoing studies for the identification of a **new chemical entity** acting as PP2A activator.

### Opportunity

Istituto Europeo di Oncologia is seeking industrial partners willing to co-develop or support drug development efforts towards the **identification of a new chemical entity acting as PP2A activator** to be used, alone or in combination with metformin, as cancer treatment.

### Principal Investigators



#### Saverio Minucci, MD

*Drug Discovery & Immunotherapy Unit Director at IEO*

- Over 15-years experience in discovery of targeted cancer drugs
- Expert in treatment and biology of haematological malignancies

Project in collaboration with Dr. Marco Foiani, *Scientific Director* of the IFOM - The FIRC Institute of Molecular Oncology.

### References

Patent Application: PCT/EP2018/063257.