Inhibiting the Mitochondrial Intermembrane Space Assembly pathway as a new approach to prevent metabolic reprogramming of therapy-resistant leukemia stem-cells.

Cancer is a complex disease caused by interactions of multiple factors, such as genetic predisposition, environmental and lifestyle influences, infectious agents and ageing. Due to the complexity of this pathology, cancer research includes basic research, strategies for prevention, development of early diagnostic tools, and translational approaches for treatment and cure. In basic cancer research "knowledge" is the key word because if you want to interfere with a biological system you must know how it works.

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by the expansion of cells that are blocked in their capacity for normal differentiation. Through biological and genetic studies, the molecular origins of leukemia and the mutations associated with this disease are being identified. These advances in understanding the biology of AML have been translated into more effective therapies, but unfortunately, for most patients, outcomes still remain poor due to primary refractory or relapsed disease. Thus, it is important to understand the mechanisms by which AML cells are or become resistant to chemotherapeutic agents. Understanding the mechanisms of resistance may lead to new combination therapies to overcome resistance or identification of patients who should be treated with alternate regimens.

A characteristic of AML respect to normal differentiated blood cells is that the first rely on mitochondrial oxidative phosphorylation as main energy source of energy. Oxidative metabolism is a complex mitochondrial process necessary to maintain and increase cellular biomass and energy production. At the same time, the highly metabolic rate determines a condition defined as "oxidative stress". During this transformation, reactive molecules that damage lipids, proteins, nuclear and mitochondrial DNA, are produced negatively affecting cell functionality. Therefore, preventing the efficient repair of mitochondrial DNA represent a novel strategy to overcome the acquired resistance of neoplastic cells, which presently hinders the success of many anticancer therapies.

APE1 is an essential enzyme in the DNA base excision repair pathway, which is responsible for repairing both nuclear and mitochondrial DNA lesions. APE1 is imported into mitochondria under oxidative stress conditions and the pathway responsible for its translocation into the mitochondria is the MIA pathway.

Based on all these elements, we are proposing an innovative strategy to selectively target therapy-resistant AML cells by inhibiting the MIA pathway as a way to prevent APE1 translocation into mitochondria and, as final consequence, to interfere with capacity of leukemic cells to repair the mitochondrial DNA. To achieve this goal, we intend to use two parallel strategies to inhibit the MIA pathway: an inhibitory peptide-based approach and a *in silico* drug screening campaign for the development of small-molecule drug-like modulators.