Mitochondria are cellular structures whose main function is the production of energy during cellular respiration. This crucial process, called oxidative phosphorylation, takes place in the respiratory chain of the inner mitochondrial membrane. Mitochondria are built of ~1500 different proteins, the sequence of the vast majority of which is encoded in the genetic material of the cell's nucleus. Only 13 proteins are encoded in the genetic material of the mitochondrion itself. Mutations in genes encoding mitochondrial proteins in both the nuclear and mitochondrial genome lead to the development of mitochondrial diseases, the symptoms of which affect primarily tissues with high energy demand such as the nervous system and muscles. To date, there is no treatment for this group of genetic diseases.

The proteasome is a protein complex responsible for selective degradation of most proteins in a cell and thus essential to maintaining intracellular balance. Mitochondrial proteins that are synthesized in the cytoplasm must be actively transported to mitochondria. Our group's research pointed to an important role of the proteasome in the control of proteins transported to mitochondria: proteins which are not properly imported may aggregate in the cytosol and induce proteotoxic stress. The immunoproteasome is an alternative version of the proteasome characterized by a different composition of subunits involved in protein degradation, which is found in immune cells where it is involved in generation of major histocompatibility complex class I peptides. Despite the abundance of the immunoproteasome in immune cells, it has been shown that it can be expressed in nonimmune cells suggesting alternative roles for this type of inducible proteasome. Our latest studies on cells with mutations in genes encoding mitochondrial proteins discovered a novel alternative form of the proteasome that overexpresses a single immunoproteasome subunit. However, the mechanism of its activation and, even more importantly, its role in cells with mitochondrial dysfunctions have not yet been determined.

In the proposed project, we plan to perform three main research tasks. In the first place, we want to characterize the conditions under which the newly identified alternative proteasome is induced. We will screen for induction of immunoproteasome specific subunits in various human cell models carrying mutations in genes encoding mitochondrial proteins, including cell lines derived from patients with mitochondrial diseases. In addition, we will treat cells with different mitochondrial stressors in order to find those able to induce overexpression of immunoproteasome-specific subunits. Secondly, we aim to identify the mechanisms involved in the activation of the mitochondrial stress-induced alternative proteasome. In particular, we will look for transcription factors involved in the formation of the mitochondrial stress-induced alternative proteasome and verify contribution of interferons to this process. The last goal is to explore the influence of the newly identified alternative proteasome on the physiology of cells with mitochondrial deficiency. This will allow us to pinpoint whether this new form of proteasome has the potential to reduce proteotoxic stress and improve cells fitness or conversely may contribute to the pathogenesis of mitochondrial diseases.

The data generated in this project will both enrich our basic understanding on the cellular responses to mitochondrial stress and provide deep insight into how mitochondrial stress may reshape the proteasome to fight proteotoxic stress. Consequently, the impact of this project will be twofold: contributing to the field of mitochondrial protein homeostasis and proposing new molecular targets for future therapies of devastating mitochondrial disorders.