Mitochondria are vital powerhouses of our cells, playing a central role in countless processes essential for our health. But to function properly, these complex organelles need to import most of their proteins from the surrounding cytosol through sophisticated molecular machines called translocases. Keeping protein import coordinated is crucial as its errors can disrupt the cell's balance and lead to serious illnesses, including neurodegenerative disorders. One key gate into mitochondria is the translocase of the outer membrane (TOM), which is also a platform for protein quality control. It works with cytosolic chaperones like HSP70 and HSP90, and the cell's waste disposal system, the ubiquitin-proteasome system, to ensure that proteins are imported correctly. When this delicate balance is disturbed, the entire cell's health is at risk.

While the TOM translocase in the common model organism yeast is well-understood, its human counterpart remains largely a mystery. Our team performed an in-depth analysis of the human TOM translocase's partners and made an exciting discovery: a previously unidentified TOM interactor BAG2. BAG2 is a fascinating protein already linked to cancer drug resistance and protein aggregation in neurodegenerative diseases. We found that BAG2 directly interacts with TRABD, a little-understood protein associated with the TOM complex that influences how certain proteins enter mitochondria. This newly discovered interaction between BAG2, TRABD, and the TOM translocase opens up a unique opportunity to explore how cytosolic proteins impact the health and stability of our mitochondria.

Our project aims to uncover the precise role of BAG2 and similar proteins in the import and quality control of mitochondrial proteins. We know that certain classes of chaperones and chaperone-associated proteins like HSP70, HSP90, and DnaJ help with protein import, but the broader picture of how other chaperone-associated proteins contribute is unclear. BAG2 is particularly promising because it helps HSP70, a key chaperone, and also directs unwanted proteins to the proteasome for degradation. Interestingly, under cellular stress, BAG2 forms clusters that attract HSP70 and components of the proteasome. This suggests that BAG2 could be a crucial link, helping the cell decide whether a protein should be imported into the mitochondria or degraded. The mechanisms governing this critical decision on the mitochondrial surface are poorly understood, and our project will significantly advance this knowledge.

Our research is exceptionally relevant, especially with recent discoveries about how mitochondria communicate their health status to the rest of the cell. These feedback mechanisms allow cells to adapt and maintain their protein balance during stress, preventing disease and neurodegeneration. We believe that BAG2 interaction with the TOM complex and TRABD could be another vital mechanism of this communication network. By understanding these fundamental processes, we move closer to finding new ways to prevent and treat conditions like Alzheimer's and Parkinson's.