The human body consists of trillions of cells, most of which produce thousands of proteins that regulate their functions and processes, ensuring the proper functioning of the body. Such a complex system must be equipped with a reliable quality control system that allows for protein monitoring during production, ensures their proper functioning, and is responsible for their repair or removal when proteins are damaged or malfunctioning. When the protein quality control systems stop functioning properly (which often occurs with aging), it contributes to the development of neurodegenerative diseases such as Alzheimer's or Parkinson's and certain cancers. One of the key elements of the protein quality control system in the cell is the chaperone protein Hsp70. Hsp70 works with its co-chaperones that regulate Hsp70's function and influence the fate of damaged proteins. Damaged, misfolded, or aggregated proteins (also called non-native) can be repaired or directed to degradation, and the decision regarding the fate of the protein is referred to as molecular triage. Hsp70 and its co-chaperones regulate balanced protein triage, to prevent premature protein degradation.

One of Hsp70's co-chaperones is the enzyme ubiquitin ligase CHIP. CHIP tags non-native proteins bound to Hsp70 with a small molecule- ubiquitin- directing them to degradation. In this way, CHIP regulates triage by promoting degradation rather than repair, but the molecular mechanism of this regulation remains largely unknown. In this project, we will investigate how the interaction between CHIP and Hsp70 regulates triage and elucidate the role of other co-chaperones and various non-native proteins in this process. To achieve this, we will use a method developed in our laboratory based on biolayer interferometry. In this method, we place a non-native protein on the surface of an optical sensor and then track how Hsp70 and its co-chaperones recognize and bind to their substrate. This method has already allowed us to explain the molecular mechanisms of cooperation between Hsp70 and co-chaperones from the J-domain protein family and nucleotide exchange factors. This time, in our research, we will focus on the influence of CHIP on Hsp70 activity, particularly on the recognition and repair of non-native proteins by Hsp70. Based on our preliminary results, we expect that CHIP disrupts these Hsp70 activities, thereby favoring the degradation of damaged proteins, but other co-chaperones competing with CHIP for Hsp70 may significantly influence this process. One of the non-native proteins studied in this project will be aggregated p53, which is responsible for the development of many cancers in humans.

Our research will provide detailed knowledge about the mechanisms regulating the degradation of damaged proteins in the cell by Hsp70 and CHIP. Understanding these mechanisms could allow for the development of therapies that utilize the existing cellular quality control systems to prevent diseases such as Alzheimer's or Parkinson's, or enable targeting damaged proteins associated with cancer, such as p53.