Each cell in human body produces proteins that are necessary for its proper functioning. Different cells can synthetize some specific proteins such as hormones, enzymes or antibodies that are secreted outside the cell. These secretory proteins play significant role in the regulation of processes important for whole organism. Proteins that are secreted as well as many others that stay inside the cell are produced in special cellular compartment called endoplasmic reticulum (ER). ER forms an interconnected network of flattened, membrane-enclosed sacs or tube-like structures. Actively working proteins have to possess proper conformation and shape, we say that they have to be properly folded. In the ER, different proteins called molecular chaperones and specific folding enzymes are involved in protein maturation. Unfortunately, despite action of the quality control folding machinery, some ER proteins cannot be folded in the right way. In consequence, they cannot work properly in the cell. Such misfolded proteins are dangerous and they must be degraded – it means broken into small peptides and then into amino acids. ER do not possess its own degradation machinery, so misfolded proteins have to be transported to the cytosol for degradation. Process that includes specific recognition of misfolded proteins in the ER and their subsequent transport to the cytosol for degradation is called ERAD (for ER-associated protein degradation). During ERAD, misfolded proteins are directed to special channels that are present in the ER membrane. Two types of the channels, Sec61 and Derlin are known currently. However, their nature and direction of certain ERAD substrates to these channels are poorly understood.

The main objective of this project is to address the question of how certain ERAD substrates are sorted to the ER conducting channels. We want to analyze the relationship between Sec61 and Derlin proteins during ERAD.

System ERAD is not used only by misfolded proteins. Some toxins and viruses that attack human cells use ERAD to be transported from the ER to the cytosol, where ultimately they will act. Moreover, degradation of some ER proteins is highly regulated by ERAD. In our project we will use different types of ERAD substrates to better understand the general mechanisms of protein substrates transport through ER channels. We will study different proteins interaction and we will analyze how higher and lower level of some ER chaperones and channel proteins influence degradation and transport of our ERAD substrates.

ERAD is a part of a protein quality control system operating in the ER, very important process determining the proper functioning of all human cells. For this reason ERAD studies became one of the central issues in current cell biology. It has been demonstrated that many human diseases can be related with improper functioning of protein quality control system and ERAD. Thus, understanding the detailed mechanisms of ERAD has dual meaning: contributes to general biological knowledge of human cells and gives possibility for practical use of this knowledge in the future. This may contribute to the improvement of health and life standards of future generations. For these reasons we have been studding ERAD for many years and results of our already published experiments contributed to the overall understanding of ER substrates recognition by molecular chaperones. Results of the experiments described in this project will broaden our general knowledge about less well understood and known aspects of ERAD – ER channels selection and protein transport from the ER to the cytosol.