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MEGCANN syndrome (*3-methylglutaconic aciduria, type VII, with cataracts, neurologic involvement and neutropenia*) is a severe multi-organ congenital disease. The patients present with a wide range of neurological symptoms, intellectual disability, cataracts, neutropenia and movement disorders. In 2015 it has been shown that the disease is caused by mutations in the gene coding for CLPB protein. So far, nothing is known on the role played by this protein in physiological processes in human. Analysis of the amino acid sequence of CLPB protein revealed that its fragment has significantly high homology to Hsp100 family of chaperones. Members of Hsp100 family of proteins are involved in protection from heat-shock in bacteria and fungi. This has been my research area at the Department of Molecular and Cellular Biology, Intercollegiate Faculty of Biotechnology, University of Gdańsk, Poland. For that reason I was invited to participate in research that led to discovery of the role of CLPB gene in pathogenesis of MEGCANN syndrome (head of the project: prof. Wevers, Radboud University Medical Center w Njmegen, The Netherlands). I was the first to obtain in vitro purified protein preparation. My input in the research provided crucial arguments supporting the role of CLPB in pathogenesis of MEGCANN syndrome what eventually lead to a joint publication being the first report on the subject matter. The impact of our research on the field can be illustrated by the fact, that our manuscript was published in prestigious American Journal of Human Genetics (currently 6/167 in respective journal category), [Wortman et al. 2015].

The current research proposal is aimed at continuation of my pioneer studies of the CLPB protein. It remains unknown, in what physiological process(es) the protein participates, what are its biochemical properties and mechanisms of action. The above mentioned similarity to Hsp100 family of proteins is restricted to a fragment of the protein only, thus it cannot give reasons for a related function of the CLPB. Nonetheless, it allows to assume some degree of structural and functional similarities. Accordingly, in the current project I am planning to evaluate biochemical properties of the human CLPB protein. Having purified CLPB protein preparation I will also aim at identification of partner proteins that cooperate with CLPB. The later would facilitate recognition of the physiological role of CLPB in the cell. In parallel to studies on physiological role of CLPB in human I am planning to perform studies of the aberrant variants of the protein resulting from pathogenic mutations detected in patients with MEGCANN syndrome. Here, selected pathogenic sequence variants of the CLPB will be purified and studied in vitro as to show what type of biochemical changes result from malfunction of particular domains of the protein.

The knowledge on the role of CLPB in physiology and disease obtained as the result of the proposed project will not only help physicians to evaluate pathogenecity as well as prognostic and predictive significance of particular mutations of the CLPB gene. It will, above all, broaden basic knowledge of human physiological processes of the cell through identification of properties of the CLPB protein and its role in yet undisclosed physiological processes.