Lipids, together with nucleic acids and proteins, are fundamental components of living organisms. Nucleic acids store and replicate genetic information. After ‘translation’ the synthesized proteins catalyze the formation of a broad array of low molecular weight products including lipids. Lipids together with proteins constitute plasma membrane which surrounds the cell ensuring its individuality and integrity and mediates cell interactions with the environment. Moreover, intracellular organelles of all eukaryotic cells are encapsulated in their dedicated lipid-protein membranes creating, together with the intracellular vesicles, a complex endomembrane system. The internal cell membranes must support the correct functioning of each of the organelles as well as the exchange of the metabolites and signaling molecules between these highly specialized cellular ‘factories’. Besides their structural role (as membrane constituents) and the function as energy stores, lipids are implicated in dozens of cellular processes, e.g. as cellular signaling molecules, hormones (testosterone, estrogen), vitamins (A, D, E), etc. It is worthwhile to remember that biotechnological applications of lipids include vesicles encapsulating drugs or genetic material (liposomes, lipid-based nanoparticles) designed to improve drug bioavailability, specificity and to decrease the toxicity of chemotherapy. Aberrations in lipid metabolism, i.e. decreased breakdown, upregulated formation, dysregulated transport, are considered causative agents of numerous human diseases, both common (hypercholesterolemia or metabolic syndrome – related to cholesterol or fatty acid metabolism) and rare ones, related to accumulation of specific lipid classes (e.g., Niemann-Pick disease). Abnormal biosynthesis of lipid called Dolichol (studied in this project) leads to aberrations in protein functions (due to aberrant protein glycosylation) which in turn leads to Congenital Disorder of Glycosylation. This is a rare genetic disease with severe neurological symptoms and developmental retardation.

Since numerous molecules produced in one organelle exert their biological activity (or are stored) in different cellular compartment or in the extracellular space they must undergo translocation and this process is mostly dependent on the intracellular vesicular transport, i.e. movement of the endomembrane transport containers. Consequently, vesicular transport is an integral part of life and perturbations of this process in humans result in diseases (e.g., cancer or Parkinson's disease). Vesicle transport and fusion operate, with the same general principles, in organisms as different as yeast, man and plant.

A growing number of data suggests that beyond their function in vesicular transport some proteins, components of the complex machinery of vesicular transport, are implicated in distinct cellular pathways. Such unexpected findings might help to find new regulatory nodes in cell metabolism and should be carefully exploited. Strikingly, observations published very recently indicate that one of proteins regulating the vesicular transport (named TRAPPC11) is implicated in protein glycosylation and possibly also in the biosynthesis of Dolichol.

This project is focused on elucidation of the processes linking Dolichol biosynthesis and vesicular transport, in particular a role of protein named TRAPPC11 in Dolichol formation. Studies on the Dolichol synthetic pathway proved that an alternative yet elusive route of Dolichol formation must exist in addition to the well-recognized biosynthetic pathway described by us and others in animal, yeast and plant cells. Clarification of the entire metabolic pathway responsible for the formation of Dolichol might help to design new therapeutic strategies for Dol-deficiency related diseases. We shall explore this aspect of cell metabolism in various eukaryotic cells. Moreover, we will study the effect of Dolichol on the properties of biological membranes.

We plan to use both, plant (Arabidopsis, an excellent model for biologists) and mammalian cells (so called cell lines) grown in the laboratory to study the role superlipid Dolichol plays in eukaryotic cells.

Taken together, we will elucidate novel cellular mechanisms interconnecting cellular processes - protein glycosylation and vesicular transport – such links have not been characterized yet. Deregulation of these processes result in serious metabolic aberrations which in humans manifest as diseases. In a longer perspective the knowledge resulting from the project might be useful for planning the strategy of maintaining the homeostasis of the cell when any of the analyzed processes is dysfunctional. Consequently, deeper understanding of the molecular basis of these processes will help to clarify the cellular background of human diseases and open new horizon for the design of therapeutic interventions.