Galectins are proteins involved in many biological functions, including immune responses, cell migration and signaling. The multiple biological functions of galectins stem from their interactions with diverse proteins and lipids that contain galactose (monosaccharide sugar) bound covalently to their functional groups. In mammals, the galectin family consists of 15 members. Galectin-3 is unique within this protein family because of its peculiar molecular architecture. Galectin-3 has been reported to be involved in numerous intra- and extra-cellular processes, including endocytosis.

Endocytosis is a cellular process in which substances are brought into the cell. The material to be internalized is surrounded by a patch of the cell membrane, which then buds off inside the cell to form a vesicle containing the ingested material. The best-characterized endocytosis pathway is controlled by the protein called clathrin. Other, clathrin-independent endocytosis processes are less understood in general. In particular, the molecular mechanisms underlying the galectin-3-dependent endocytosis remain elusive. Very recently, however, galectin-3 has been demonstrated to undergo liquid-liquid phase separation (LLPS), which sheds new light on how this protein can perform its biological functions.

LLPS of biomolecules underlies the formation of membraneless organelles and other biomolecular condensates, which is currently a subject of intense research. LLPS has been recognized as an important organizing phenomenon in cells. Our hypothesis is that LLPS of galectin-3 at the cell membrane provides a driving force for membrane bending toward the cytosol and, thus, enables the galectin-3-dependent endocytosis. The objectives of our project are the following: (i) to explore the intra- and inter-molecular interactions that drive the LLPS of galectin-3, (ii) to give a detailed description of the molecular architecture of galectin-3 condensates in aqueous solutions and at membrane surfaces, and (iii) to explain the molecular mechanisms underlying the membrane bending and endocytic pit formation by the galectin-3 biomolecular condensates. We will use state-of-the-art molecular dynamics methods to reach the project objectives.

Galectin-3 is shuttled between the cytoplasm and the nucleus. It is also secreted to the cell surface and into extracellular fluids. The different locations of galectin-3 contribute its diverse functions, which include – but are not limited to – cell growth, cell adhesion, apoptosis and mRNA processing. Since galectin-3 is involved in numerous biological functions, it is also an important molecular player in different disease states and cell-pathogen interactions. In fact, galectin-3 has been identified as a biomarker for disease diagnosis and a target for therapy. In particular, galectin-3 overexpression and changes of sub- and inter-cellular localization are commonly seen in various types of cancers. More and more evidence indicates that galectin-3 is involved in regulation of a myriad of cancer cell activities during cancer development, progression and metastasis. Since our project will significantly contribute to biomolecular research on galectin-3, it may directly influence future developments in cancer treatments.