Principal Investigator: **Ludger JOHANNES**

Grant Title: **Glycan topology switch to regulate integrin activity**

Progress Report:

(a) Abstract:

It is commonly assumed that the glycan makeup of glycoproteins is final and static once these have reached the cell surface. In the research program that was co-financed by the Mizutani Foundation, we have challenged this notion by the discovery of two molecular switches which induce acute and reversible changes of glycan structure or arrangement in space. The two switches have a common denominator - the unexpectedly dynamic nature of glycans at the cell surface to drive endocytosis and repurposing of membrane glycoproteins.

In a first part of the program, we have discovered how the epidermal growth factor induces local removal of sialic acids (desialylation) to enhance binding of galectins and drive endocytosis - termed Desialylation GlycoSwitch. In a second part of the program, we have discovered how dynamic changes in N-glycan arrangements in space triggered by conformational state changes of membrane glycoproteins (here: integrins) drive nucleation of galectin oligomers and endocytosis - termed Conformational GlycoSwitch.

The striking novelty of these findings lies in the dynamic regulation of the glycan landscape at the cell surface to achieve select recruitment and internalization of membrane glycoproteins. Importantly, although the two mechanisms by which galectin-mediated endocytosis is acutely regulated are complementary, they may not be mutually exclusive and could indeed cooperate. Individually the two GlycoSwitch studies provide unique insights into the basic cellular processes of cell signaling and trafficking that by themselves will have a strong impact in the life sciences.

Specifically, in the context of the Desialylation GlycoSwitch framework, we discovered a novel facet of EGF signaling, a previously unexplored pH-triggered enzymatic mechanism at the plasma membrane, and a regulatory circuit that links growth factor-induced desialylation of glycoproteins at the plasma membrane to their resialylation in the Golgi and repurposing of their functions. In the context of the Conformational GlycoSwitch framework, we discovered the true nature and shape of galectin-3 oligomers. We identified galectin-3 as the first specific functional interactor of the bent-closed inactive conformational state of integrins, a milestone in the investigation of these important cell adhesion and migration proteins. We also identified a structural pattern that is common to diverse processes of lectin-dependent endocytosis, which breaks new ground in membrane trafficking.