Lipid scrambling is vitally important at multiple physiological levels, from blood clotting, clearance of apoptotic cells and diurnal phagocytosis of photoreceptor outer segments in the retina, to the growth of cell membranes and protein glycosylation in the endoplasmic reticulum. Some years ago, we discovered that the visual pigment rhodopsin – well known as a G protein--coupled signaling receptor (GPCR) – is a constitutively active phospholipid scramblase capable of translocating phospholipids rapidly across a membrane bilayer. The scramblase activity of rhodopsin – also a property of other Class-A GPCRs – is critical for disc membrane homeostasis because it corrects the trans-bilayer phospholipid imbalance caused by the unidirectional lipid pumping activity of disc-localized ATP-driven transporters, including the ‘Stargardt’s disease transporter’ ABCA4. The molecular mechanism of lipid scrambling is not fully understood. Mutagenesis experiments revealed that an opsin monomer is capable of scrambling lipids. Atomistic molecular dynamics (MD) simulations of opsin embedded in a membrane bilayer identified a pathway for lipid translocation along the interface between specific transmembrane helices of the protein. From these results we determined structural and dynamic features of the protein that are mechanistically involved in lipid translocation, and generated quantitative models for the kinetics of the translocation process. The mechanistic insights and predictions emerging from these computational studies are being used to guide the design of opsin mutants with defined scrambling activity that can probe and refine the mechanistic models.

Wednesday, March 1\textsuperscript{st}, 2017, h 16:00
University of Zürich – Irchel, room Y03 G95
Winterthurerstrasse 190, 8057 Zürich

The lecture will be hosted by Prof. Raimund Dutzler (UZH)