ESRF	**Experiment title:** Amyloid cross-interactions at lipid membranes	**Experiment number**: SC-2925
Beamline: ID 10B	**Date of experiment**: from: 31/03/2010 to: 06/04/2010	**Date of report**: 15/02/2011
Shifts: 18	**Local contact(s)**: Dr. Oleg Konovalov	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Florian Evers,*[,1] Christoph Jeworrek,* Mirko Erlkamp,* Sebastian Grobelny,* Metin Tolan,[1] and Roland Winter

Technische Universität Dortmund, Fakultät Chemie, D-44221 Dortmund

[1] Technische Universität Dortmund, Fakultät Physik/DELTA, D-44221 Dortmund

Protein aggregation has severe implications in diseases like Alzheimer's and Parkinson's disease, or in affecting peripheral tissues as in the case of type-II diabetes mellitus.[1] Several studies have shown that lipid-peptide interactions can play a crucial role in the fibril formation of human islet amyloid polypeptide (IAPP) and amyloid ß (Aß). [2-5] For example, the interaction of IAPP especially with anionic (DOPC/DOPG) [2,3] or raft membranes (DOPC/DPPC/cholesterol) [3-5] and the interaction of Aß with neuronal lipid membranes foster fibrillation. Exploiting cross-amyloid interactions, it has been shown that a non-amyloidogenic mimic of IAPP is able to block also Aß cytotoxic self-assembly, hinting at a molecular link between Alzheimers' disease and type-II diabetes mellitus. [6] Therefore, cross interactions between IAPP and Aß might affect the fibrillation pathways of both proteins. [7]

Here, we focus on the interaction of IAPP and Aß with a complex model membrane system comprising DOPC, DOPG, DPPC, DPPG, and cholesterol. This novel model membrane system combines anionic and raft features. Applying X-ray reflectometry (XRR), grazing incidence X-ray diffraction (GIXD), and surface tensiometry, a complete molecular-scale picture of the membrane-mediated peptide oligomerization and fibril formation as well as of cross-amyloid interactions in the presence of lipid membranes is obtained.

The experiments were performed with the liquid surface scattering set-up of ID10B at ESRF. The lipid mixture was spread at the air-water interface in a Langmuir trough, which was previously filled with aqueous buffer or peptide solution. Then, the lipid raft film was compressed to an initial surface pressure of 30 mN m^{-1}, mimicking the outer leaflet of

biological membranes; the lateral area available for the lipid film was kept constant, and measurements were started. During the measurements, the time-dependent development of the lateral film pressure was monitored and structural changes of the lipid film were investigated by subsequent XRR and GIXD scans, as exemplarily shown in Figures 1 and 2. The results obtained represent a significant contribution to elucidating the mechanism of amyloid-cross interactions in the presence of aggregation-fostering anionic lipid raft membranes and will thus help understanding amyloidogenesis *in vivo*.

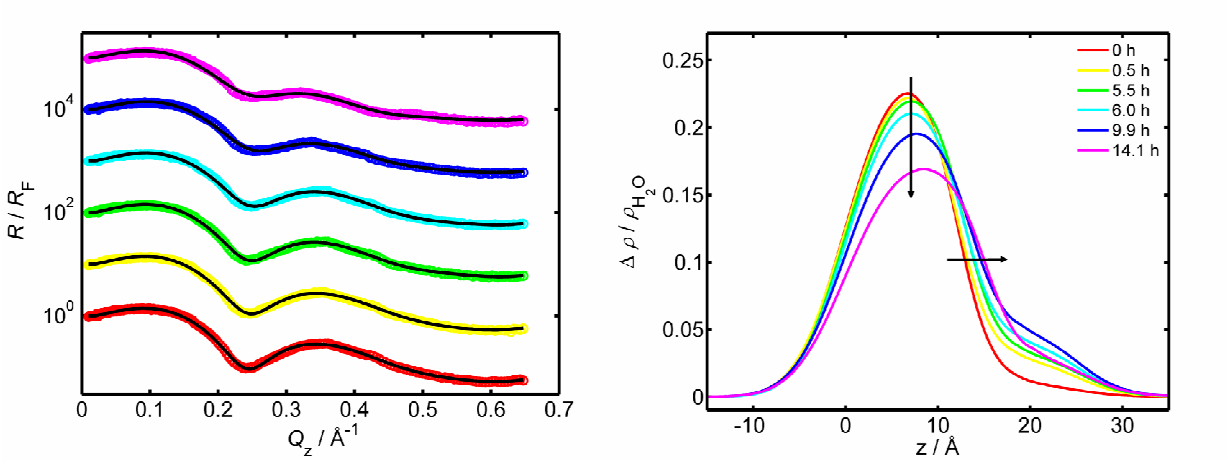

Figure 1: Left: Exemplary XRR data (open symbols) with fits (solid lines) based on a two-layer model of the anionic lipid raft monolayer in the presence of Aß. The XRR curves are shifted along the y-axis with increasing time. Right: Time evolution of the reduced electron density profiles (EDPs) of the XRR curves. Temporal changes of the lipid head and tail groups are indicated by black arrows. To retrieve the reduced EDPs, the EDP of the air-water interface has been subtracted.

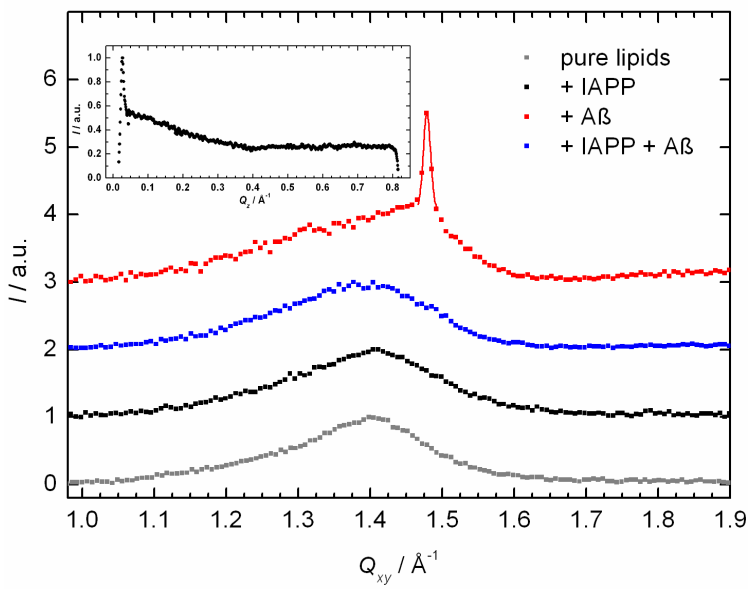

Figure 2: GIXD patterns $I(Q_{xy})$, obtained by integrating along Q_z, of anionic lipid raft monolayers on different peptide subphases. For clarity, data are shifted vertically. For all systems (except Aß), only one peak per lipid phase can be found, indicating a hexagonal packing of the lipids. For Aß, the coexistence of two different crystalline lipid domains is observed. Inset: Typical Bragg rod intensity profile $I(Q_z)$. The absence of a peak at $Q_z \neq 0$ indicates little or no molecular tilt of the lipid tails.

[1] F. E. Cohen, J. W. Kelly, *Nature* **426** (2003) 905. [2] F. Evers, C. Jeworrek, M. Tolan, R. Winter, et al. *J. Am. Chem. Soc.* **131** (2009) 9516. [3] S. Jha, D. Sellin, R. Seidel, R. Winter *J. Mol. Biol.* **389** (2009) 907. [4] K. Weise, D. Radovan, A. Gohlke, N. Opitz, R. Winter, *ChemBioChem* **11** (2010) 1280. [5] C. Jeworrek, K. Weise, R. Winter, F. Evers, M. Tolan, *ESRF Experimental Report* SC-2709 (2009). [6] L.-M. Yan, A. Velkova, M. Tatarek-Nossol, E. Andreetto, A. Kapurniotu, A. *Angew. Chem.* **46** (2007) 1246. [7] E. Andreetto, L.-M. Yan, M. Tatarek-Nossol, A. Velkova, R. Frank, A. Kapurniotu, *Angew. Chem.* **49** (2010) 3081.