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Abstracts

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Plenary talks

O-001
View into the ribosomal exit tunnel
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Ribosomes, the universal polymerases for the translation of the genetic code into proteins, possess an elongated tunnel through which the nascent protein progress until they emerge into the cell. While traveling through the tunnel the nascent proteins can interact with specific tunnel wall components capable of imposing transient or a relatively long elongation arrest. Furthermore, internal architecture and flexibility allow response to cellular signals, thereby provides a mechanism for gene regulation.

O-002
The interplay between actin dynamics and membrane tension determines the shape of moving cells
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A central challenge in cell motility research is to quantitatively understand how numerous molecular building blocks self-organize to achieve coherent shape and movement on cellular scales. We focus on one of the classic examples of such self-organization, namely lamellipodial motility, in which forward translocation is driven by a treadmilling actin network. We combine detailed measurements of lamellipodial morphology, spatio-temporal actin dynamics and membrane tension, with mathematical modelling to explain how global shape and speed of the lamellipodium emerge from the underlying assembly and disassembly dynamics of the actin network within an inextensible membrane bag.

O-003
Structure determination of dynamic macromolecular complexes by single particle cryo-EM
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Macromolecular complexes are at the heart of central regulatory processes of the cell including translation, transcription, splicing, RNA processing, silencing, cell cycle regulation and repair of genes. Detailed understanding of such processes at a molecular level requires structural insights into large macromolecular assemblies consisting of many components such as proteins, RNA and DNA. Single-particle electron cryomicroscopy is a powerful method for three-dimensional structure determination of macromolecular assemblies involved in these essential cellular processes. It is very often the only available technique to determine the 3D structure because of the challenges in purification of complexes in the amounts and quality required for X-ray crystallographic studies.
In recent years it was shown in a number of publications that it is possible to obtain near-atomic resolution structures of large and rigid macromolecules such as icosahedral viruses. Due to a number of methodological advances there are now also great perspectives for high-resolution single particle cryo-EM studies of large and dynamic macromolecules. Successful high-resolution structure determination of dynamic complexes requires new biochemical purification strategies and protocols as well as state of the art electron microscopes and high-performance computing. In the future cryo-EM will thus be able to provide structures at near-atomic

Forming Domain (218-289) from the fungi *Podospora anserina*, which is not toxic in yeast. Some toxic amyloids mutants were generated by random mutagenesis. *In vitro* the most toxic mutant called "M8" displays very peculiar nanofibers, which polymerized mainly in amyloid antiparallel β-sheets whereas the non-toxic WT exhibits a parallel polymerization. We further established the dynamic of assembling of the M8 toxic amyloid, in comparison to the WT non-toxic amyloid, and showed the presence of specific oligomeric intermediates also organized in antiparallel β-sheet structures. A more global structure/toxicity study on more than 40 mutants clearly identified an antiparallel β-sheet signature for all the toxic mutants. Therefore size, intermediates and antiparallel structures may account for amyloid toxicity in yeast but we still wonder what their cellular targets are. Recently, we established the first evidences that toxic mutants may specifically bind *in vitro* to lipids, particularly negatively charged.

P-203

Interconnected mechanisms in Abeta(1-40) peptide fibril formation

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We present an experimental study on the fibril formation of Aβ(1-40) peptide at pH 7.4. The kinetics of this process is characterized by the occurrence of multiple transient species that give rise to final aggregates whose morphology and molecular structure are strongly affected by the growth conditions. To observe in details the aggregation pathway as a function of solution conditions, we have used different experimental techniques as Light scattering, Thioflavin T fluorescence, Circular Dichroism and two-photon fluorescence microscopy. This approach gives information on the time evolution of conformational changes at molecular level, on the aggregates/fibrils growth and on their morphologies. The selected experimental conditions allowed us to highlight the existence of at least three different aggregation mechanisms acting in competition. A first assembly stage, which implies conformational conversion of native peptides, leads to the formation of small ordered oligomers representing an activated conformation to proceed towards fibril growth. This process constitutes the rate limiting step for two distinct fibril nucleation mechanisms that probably implicate spatially heterogeneous mechanisms.

P-204

Amyloid formations and interactions

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The formation of amyloid fibrils of amylin 10-29 was studied by means of molecular dynamics (MD) and energy partition on three peptide ß-sheet stack systems with the same amino acid composition: wild type amylin 10-29 (**Amyl 10-29**), reverse amylin 10-29 (**Rev-Amyl 10-29**) and scrambled amylin version **Scr-Amyl 10-29**. The results show that for Amylin10-29 peptides, amino acid composition determines the propensity of a peptide to form amyloid fibrils independent of their sequence. The sequence of amino acids defines the shape and the strength of amyloid protofibril, which conforms with the atom force microscope (AFM) data [1]. MD show that the 6x6RevAmyl-10-29 stack has looser self-assembly than the 6x6Amyl-10-29 stack, which conforms with the results of Fourier transform infrared spectroscopy (FTIR) measurements for the peptides studied [1]. The results of MD show that 6x6Amyl-10-29 could have a turn, which consists with FTIR data [1].

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Reference

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O-205

Mechanistic insights into Aβ42 aggregation and effects of inhibitors

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Data on Aβ aggregation kinetics have been characterized by a large spread between experiments on identical samples that contain so many molecules that stochastic behaviour is difficult to explain unless caused by uncontrolled amounts of impurities or interfaces. We have therefore spent considerable effort to eliminate sources of inhomogeneity and reached a level of reproducibility between identical samples and between experiments on separate occasions that we can now collect data that can lead to mechanistic insights into the aggregation process per se, and into the mechanism of action of inhibitors. Data on Aβ42 aggregation will be shown that give insight into the influence of physical parameters like peptide concentration, shear and ionic strength, as well as the effect of inhibitory proteins, model membranes and the effects of sequence variations. Monte Carlo simulations of amyloid formation from model peptides corroborate the finding from experiments and underscore that the very high level of predictability and reproducibility comes from multiple parallel processes.
References: Hellstrand et al *ACS Chem Neurosci.* 1, 13-18 (2010); Hellstrand et al, Biophys J. 98:2206-2214 (2010); Cabaleiro-Lago et al, *ACS Chem Neurosc., 1, 279-287* (2010)