Hsp90 binds to and promotes the clearance of tau, which is thought to reduce the formation of neurotoxic aggregates. Tau is an intrinsically disordered protein and it is unclear what role, if any, Hsp90 has in controlling its structure and dynamics. Hsp90 cooperates with numerous co-chaperones such as the immunophilin FKBP51, which assists in regulating the folding and processing of client proteins like tau. Defining the precise interactions between tau and the Hsp90 chaperone network is important for understanding the role of tau in Alzheimer’s Disease. In this study, nuclear magnetic resonance (NMR) spectroscopy was used to probe the interaction between 15N-labeled tau, Hsp90 and FKBP51. The results demonstrate that two hydrophobic hexapeptide motifs located at residues 275-280 and 306-311 in tau’s C-terminus bind to Hsp90 and FKBP51. This was determined by observing a significant reduction in the intensity ratios of HSQC spectra for free tau and tau in complex with Hsp90 and FKBP51. Resonances that show reduced intensities in the absence of line broadening are probably undergoing chemical exchange with a bound conformation. Several residues near the N-terminus of the protein also show a similar reduction in intensity upon addition of Hsp90 and FKBP51. Formation of the ternary complex around the client protein tau is congruent with currently proposed models suggesting that the binding of FKBP51 and Hsp90 assist in tau regulation, thereby triggering its recycling back to the MT surface.

1988-Pos Board B7
Single Molecule AFM Force Spectroscopy Analysis of Alpha-Synuclein Misfolding
Alexey V. Krasnoslobodstev, Jie Peng, Ivan Volkov,
Jean-Cristophe Rochet, Yuri Lyubchenko
1Jing-Jing Zhou1, Jie Peng2, Ivan Volkov3,
Universität Zürich, Zürich, Switzerland, 2Saint Petersburg State University, Saint Petersburg, Russian Federation, 3Max Planck Institute for Biophysical Chemistry, Göttingen, Germany.

Protein misfolding is a transient state during self-assembly into aggregates defining the molecular mechanism of the development of Alzheimer’s, Parkinson’s and other neurodegenerative diseases. Misfolding and aggregation of alpha-synuclein (a-Syn) is tightly linked to the development of Parkinson’s disease. Here we applied single molecule AFM force spectroscopy (SMFS) to probe transient misfolded states of a-Syn measuring pair-wise interactions between individual a-Syn molecules at conditions that induce conformational transitions associated with enhanced aggregation. In the SMFS approach we probed the interactions between a-Syn covalently attached to the AFM probe and substrate by the C-terminal cysteine. We show that at conditions close to physiological, addition of spermidine results in dramatic increase of the protein’s propensity to misfold. Additionally, using SMFS we detected and characterized misfolded dimers of a-Syn, the simplest aggregated form of a-Syn. Our results demonstrate that more than one segment within the protein molecule is responsible for the initial association of a-Syn into dimers and potentially into higher-order polymers and fibrils. This finding suggests that even the first step of a-Syn self-assembly (dimerization) possesses a certain degree of heterogeneity. We hypothesize that these different misfolded conformations can lead to different types of oligomers and define the aggregation pathway. The marked differences in the misfolding patterns between WT a-Syn and single point mutants might be responsible for the higher propensity of the mutants to aggregate and cause early-onset PD.

The work was supported by grants to YLL from National Institutes of Health (1R01GM091743-01A1 and 1R01 GM90603-01A1), U.S. Department of Energy Grant DE-FG02-08ER64579, National Science Foundation (EPS - 1004094) and the Nebraska Research Initiative.
flanking sequences from huntingtin. Also, we show that electrostatic repul- 
sions due to these residues retard the rate of monomer loss and large, linear, 
ordered clusters are formed. Our observations provide a unifying framework, 
capturing all known features of the early stages of aggregation in polyglut- 
amine containing systems.

1992-Pos Board B11
A Class of Self-Assembling Aliphatic Ultrasmall Peptides as a Model 
System for Understanding and Preventing Amyloidosis
Anupama Lakshmanan1, Daniel W. Cheong2, Christian Riekel1, 
Charlotte A.E. Hauser1.
1Institute of Bioengineering and Nanotechnology, Singapore, Singapore, 
2Institute of High Performance Computing, Singapore, Singapore, 
3European Synchrotron Radiation Facility, Grenoble, France.
Core sequences of 4-6 residues that form amyloid fibrils have been identified 
within natural amyloid proteins. However, the mechanism of amyloid aggrega-
tion remains unclear. We designed a new class of aliphatic peptides (with 3-6 
residues) that self-assemble in water to amyloid β-type fibers via aβ-helical 
termediates. We compared the self-assembly of our designed peptides with 
core sequences in Amyloid-beta, Amylin and Calcitonin using a multimodal ap-
proach. A common feature was the appearance of aα-helical intermediates before 
the final β-turn structures. Another amyloid-beta core sequence containing the 
diphenylalanine motif was chosen to evaluate the role of aromatic residues in 
self-assembly. The repeated occurrence of aromatic residues in core sequences 
has led to widespread conclusions about their key role in driving self-assembly. Sur-
prisingly, the diphenylalanine-containing sequence did not form cross-β aggregates 
or involve the α-helical intermediate step. Our study puts forth a new, simplified 
model system to study amyloidosis and indi-
cates that aromatic interactions are not as important as previously postulated. The re-
sults provide valuable insight into the early intermediates and factors driving self-assembly, which is necessary for develop-
ing small molecule therapeutic drugs that prevent amyloidosis.

1993-Pos Board B12
Discrete Molecular Dynamics Study of Oligomer Formation by 
N-Terminally Truncated Amyloid B-Protein
Derya Meral, Brigita Urbanc.
Drexel University, Philadelphia, PA, USA.
Alzheimer’s disease (AD) is strongly linked to amyloid b-protein (Ab). Two 
predominant alloforms, Ab1-40 and in particular Ab1-42, are known to 
form toxic oligomers. The N-terminally truncated, pyroglutamated forms of 
Ab1-36 and Ab1-38 are highly resistant to β-proteinase degradative, and can 
seed Aβ aggregation. Discrete molecular dynamics (MDM) simulations previ-
ously captured in vitro derived distinct Ab1-40 and Ab1-42 oligomer size 
distributions and predicted that the more toxic Ab1-42 oligomers had more 
flexible and solvent exposed N-termini than Ab1-40 oligomers. Here, oligo-
mer formation by four N-terminally truncated Ab peptides: Ab3-40, 
Ab3-43, Ab1-42, and Ab1-41 were examined by the DMD approach. In 
our simulations, the four N-terminally truncated peptides showed increased 
oligomerization propensity, consistent with their in vitro tendency to seed ag-
gregation. Conformations formed by Ab1-40 had the lowest b-strand and the 
highest turn content. The tertiary and quaternary structure of Ab3-4X oligo-
mers was distinctly different from that of Ab1-4X oligomers. Ab3-4X olig-
omers were characterized by more disordered and solvent exposed N-termini 
than oligomers formed by the full-length peptides. In contrast, in comparison 
with Ab1-4X, Ab1-4X oligomers had a more compact structure, facilitated by 
Val12, resulting in less flexible and less solvent exposed N-termini, suggest-
ing reduced Ab1-4X-mediated toxicity. This unique behavior of the 
N-termini in Ab peptides might provide a plausible explanation for the exper-
imentally observed increased toxicity of Ab3-4X peptides and their pyroglu-
tamated forms.

1994-Pos Board B13
Intrinsic Disorder and Chaperon-Like Activity of Different Caseins
Silvia Vilasi, Rita Carrotta, Giacoma Cinzia Rappa, Pier Luigi San Biagio, 
Donatella Bulone.
Institute of Biophysics, CNR, Palermo, Palermo, Italy.
Casein is the best characterized milk protein and constitutes over 70-80% of 
total bovine milk protein. In milk, casein exists as large micelle-like particles 
that comprise four unrelated proteins (αs1-, αs2-, β- and κ-casein) and calcium 
phosphate. Although αs1-, αs2-, β- and κ-casein present important structural 
differences, all of them adopt extremely open and flexible conformations, 

1995-Pos Board B14
Cellular Polymamines Promote Amyloid-Beta Peptide Fibrillation and 
Modulate the Aggregation Pathways
Jinghui Luo1, Chien-Hung Yu2, Huaixin Yu2,3, Rok Borstnar4,5, 
Shina C.L. Kamerlin1, Astrid Gräslund1, Jan Pieter Abrahams1, 
1Gorlaeus Laboratory, Leiden Institute of Chemistry, Leiden University, 
Leiden, Netherlands, 2Leiden/Amsterdam Center for Drug Research, Leiden 
University, Leiden, Netherlands, 3Department of Pharmacy and 
Pharmacology, Slotervaart Hospital/the Netherlands Cancer Institute, 
Amsterdam, Netherlands, 4National Institute of Chemistry, Hajdrihova, 
Slovenia, 5Department of Cell and Molecular Biology (ICM), Uppsala University, 
Uppsala, Sweden, 6Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden.
The cellular polymamines spermine, spermidine, and their metabolic precursor 
putrescine, have long been associated with cell-growth, tumor-related gene regu-
lations, and Alzheimer’s disease. Here, we show by in-vitro spectroscopy and 
AFM imaging, that these molecules promote aggregation of amyloid-beta (Aβ) 
peptides into fibrils and modulate the aggregation pathways. NMR measure-
ments showed that the three polymamines share a similar binding mode to mono-
meric Aβ(1-40) peptide. Kinetic ThT studies showed that already very low 
polyamine concentrations promote amyloid formation: addition of 10 μM sper-
mine (normal intracellular concentration is ~1 mM) significantly decreased the 
lag time and transition times of the aggregation process. Spermidine and putrescine 
additions yielded similar but weaker effects. CD measurements demonstrated 
that the three polymamines induce different aggregation pathways, involving dif-
ferent forms of induced secondary structure. This is supported by AFM images 
showing that the three polymamines induce Aβ(1-40) aggregates with different 
morphologies. The results reinforce the notion that modulation of the Aβ pep-
tide aggregation pathways towards minimally toxic ones by addition of suitable 
ligands may be a possible therapeutic strategy for Alzheimer’s disease.

1996-Pos Board B15
Cyclic N Terminal Fragment of Amylin Forms Non Amyloid Fibers: 
Implications for Intra- and Inter-Molecular Interactions in Amylin 
Stephanie M. Cope1,2, Sandip Shinde1, Robert B. Best4, 
Ghirlanda Giovanna1, Sara M. Vaiana1,2.
1Center for Biological Physics, Arizona State University, Tempe, AZ, USA, 
2Department of Physics, Arizona State University, Tempe, AZ, USA, 
3Department of Chemistry and Biochemistry, Arizona State University, 
Tempe, AZ, USA, 4Department of Chemistry, University of Cambridge, 
Cambridge, United Kingdom.
Islet amyloid polypeptide (IAPP), also known as amylin, is a 37-residue intrin-
scally disordered hormone peptide that is secreted together with insulin by 
the beta cells of the pancreas, and is involved in glucose regulation and gastric 
emptying. IAPP is implicated in the pathogenesis of diabetes type II, due to 
its deposition in the form of amyloid fibers in the beta cells of the pancreas, 
where insulin is produced. IAPP contains a highly conserved, functional disul-
fide bond that confers a short ring-like structure (N-loop) to the N-terminus of 
the peptide. Removal of this functional element alters both the mass per length 
distributions of IAPP fibers and the kinetics of fibril formation. The mecha-
nism by which the N-loop affects IAPP aggregation is not yet understood,