This was the fourth in a series of symposia (2009, 2013 and 2016) concerned with this important area of research. The symposium featured 8 speakers (one from Sanofi, France) and 8 poster presentations. The emphasis was on gaining a better understanding of the molecular processes that govern normal brain function and dysfunction. The presenters explained how their findings could translate into new therapeutic agents for brain disorders such as Alzheimer's and Parkinson's disease.

There were good interactions between the speakers and delegates and the posters initiated lively discussions during lunch and during the refreshment breaks.

Developing Biotherapeutics for Neurological Disorders

A stimulating one-day program 10 0 1 313.98 Tf1 0 0.00000912 0 612 792 reW*nBT/F2 13.98 Tf1 0 0 1

The Molecular Origins of Neurodegenerative Disorders and the Rational Development of Therapeutic Strategies

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Interest in protein misfolding, aggregation and amyloid formation has developed with extraordinary rapidity in recent years, such that this area of science is now a major topic of research across a wide range of disciplines. The reason for this surge of interest is primarily a result of the links between amyloid formation and a range of rapidly proliferating neurodegenerative disorders including Alzheimer's and Parkinson's diseases. This talk will discuss recent progress from our laboratory towards understanding the structural and physical properties of protein aggregates, the kinetics and mechanism of the process of their formation, and the nature and origins of their links with disease. In addition, the talk will discuss the ways in which protein aggregation and amyloid formation may be inhibited or suppressed, both to understand the nature of protein homeostasis in naturally functioning organisms and also to use this information to promote the development of effective strategies through which to combat the onset and progression of neurodegenerative disorders.

T.P.J. Knowles, M. Vendruscolo and C.M. Dobson. "The Amyloid State and its Association with Protein Misfolding Diseases", Nature Rev Mol Cell Biol 15, 384-396 (2014).

S.I. Cohen et al., "A Molecular Chaperone Breaks the Catalytic Cycle that Generates Toxic Aβ Oligomers", Nat Struct Mol Biol, 22, 207-213 (2015).

F. Chiti and C.M Dobson, "Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade", Annu Rev Biochem, 86, 27-68

SAR by kinetics for drug discovery in protein misfolding diseases

Michele Vendruscolo

Centre for Misfolding Diseases
Department of

Tau self-assembly: a key

The

Poster Abstracts

Exploring the links between the oral microbiome, ageing and sporadic Alzheimer's disease.

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Abstract

Oral bacteria have been implicated in Alzheimer's disease (AD) from

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Alpha-synuclein (αSyn) is known to be involved in the neurodegenerative disorder Parkinson's disease (PD) which affects 10 million people worldwide. Patients show multiple motor (e.g. tremor, lack of coordination) and non-motor (e.g. depression, anxiety) symptoms, as well as pathological symptoms which are characterised by the loss of dopaminergic neurons and the formation of aggregated αSyn-containing Lewy bodies in the brain. Understanding the process of amyloid formation from the intrinsically disordered monomer αSyn to the complex β-sheet rich fibrils

peptides are found for a longer time in an oligomeric state.

Discussion: The glycation of Abeta 40 and Abeta42 has a strong impact on their structural stability and behavior [3]. The slower aggregation kinetics upon glycation translates into the stabilization of oligomeric forms, considered more toxic than the amyloids. These results could explain the higher incidence of AD in T2D patients.

Conclusions: Post-translational modifications can affect the structural behavior of aggregation-prone proteins and might be used to interfere with the development of AD and T2D.

Watson GS, Craft S: Insulin resistance, inflammation, and cognition in Alzheimer's Disease: lessons for multiple sclerosis. *J Neurol Sci.* 2006;245(1-2):21-33.

Sasaki N, Fukatsu R, Tsuzuki K, Hayashi Y, Yoshida T, Fujii N, et al. Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *Am J Pathol.* 1998;153(4):1149-55

Iannuzzi, C., et al: Differential effects of glycation on protein aggregation and amyloid formation *Front Mol Biosci.* 2014 1: 9.

indicated that that this interaction is protective against aggregation, considering these finding with existing literature prompted speculation that the interactions observed in SMFS may indeed be physiologically relevant.

By utilising PRE NMR experiments, we have also shown that in conditions which promote aggregation, the key N-terminal region identified in SMFS studies makes more distil intramolecular contacts, further indicating the importance of this region in the modulation of aggregation. These results may therefore present an important finding in regards to targeting the aggregation process with disease modifying agents.

The inhibition of alpha synuclein aggregation using a novel peptide-based inhibitor

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Alpha synuclein (aSyn) is a 140-residue protein localized at the presynaptic terminals. ASyn's physiological function remains poorly understood, yet it is a key player in Parkinson's disease (PD) and other neurodegenerative diseases. Disease progression is caused by the progressive loss neurons in the brain. Cell death appears to be associated with the aberrant aggregation of aSyn, and thus the inhibition of aggregation represents an enticing therapeutic strategy. Here we employ NMR to probe interactions between aSyn and a 10-residue peptide that has been previously shown to reduce aSyn fibril formation and associated cell toxicity (Cheruvara et al. 2015). Using a series of NMR timecourse experiments we show that a structural rearrangement of the peptide occurs and that this may be of importance for binding to higher-order aSyn species. Electron microscopy shows the presence of more numerous yet much shorter fibrils when aSyn is incubated in the presence of the peptide, implying that the peptide prevents fibril extension. We hypothesize that binding of the peptide impedes the formation of the aSyn species responsible for cell toxicity. We now aim to elucidate the cellular pathways involved through the use of NMR metabolomics, using our previously published SH-SY5Y neuroblastoma metabolic profiles (Phelan et al. 2017).

Bibliography:

Cheruvara, H. et al., 2015. Intracellular screening of a peptide library to derive a potent

peptide inhibitor of α-synuclein aggregation. *Journal of Biological Chemistry*, 290(12), p.jbc.M114.620484. Available at: http://www.jbc.org/content/290/12/7426.short [Accessed October 6, 2015].

Phelan, M.M. et al., 2017. Using an NMR metabolomics approach to investigate the pathogenicity of amyloid-beta and alpha-synuclein. *Metabolomics*, 13(12), p.151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29142509 [Accessed November 17, 2017].

Tau self-assembly: a key target.

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Tau is a natively unfolded protein that self-assembles to form neurofibrillary tangles (NFTs) in Alzheimer's disease and other tauopathies. Tau performed many functions in the cell within the cytoplasm and nucleus. However, during the progress of disease, tau accumulates intracellularly as NFTs composed of paired helical filaments (PHF) and straight filaments (SF) composed of a cross beta structure. Major advances have been made recently with the description of the cryo-EM structure of these filaments isolated from brain tissue. Tau assembly and disassembly has become a major target for the development of therapeutics to treat AD, including the development of a methylene blue derivative (methylthioninium) as well as immunotherapies targeting tau.

The trigger and the mechanism of tau self-assembly in vivo remains unclear. Using a truncated form of tau, we have defined specific conditions required to form PHF and SF that mimic those found in AD patients. Furthermore, we have utilised these model structures to examine the details of the mechanism by which a methylene blue derivative is able to prevent self-assembly in vitro, providing

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Coates, T. A., Woolnough, O., Masters, J. M., Asadova, G., Chandrakumar, C., & Baker, M. D. (2015). (11), 2337-2349. doi:10.1007/s00424-015-1696-2
Hodgkin, A. L., & Katz, B. (1949). (1-2), 240-249.
Kanagaratnam, M., Pendleton, C., Souza, D. A., Pettit, J., Howells, J., & Baker, M. D. (2017). (11), 3471-3482. doi:10.1113/jp273963