MS45.O03

Structural biology of Alzheimer's disease

L. Miles[1], G. Crespi[1], T. Nero[1], M. Parker[1]
[1]*St. Vincent's Institute of Medical Research, Melbourne, Australia*

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in humans with age being the biggest risk factor. The mechanisms by which the disease progresses to cognitive decline in the sufferer are complex and not fully elucidated. A defining pathological feature is the deposition of extracellular plaques composed primarily of misfolded amyloid beta (Aβ) peptide: a proteolytic breakdown product of the much larger Amyloid Precursor Protein. While Aβ peptides are the main constituents of amyloid plaques that burden the diseased brain, plaque burden correlates poorly with the severity of the disease. There is accumulating evidence that a prefibrillar or protofibrillar soluble form of Aβ can compromise neuronal functions and trigger cell death. Immunotherapy targeting Abeta is a promising direction in AD research with active and passive immunotherapies shown to lower cerebral Aβ levels and rescue cognitive function in animal models. Anti-Aβ immunotherapies are a significant class of AD therapeutics currently in human clinical trials. We have been examining the molecular basis of antibody engagement of Aβ epitopes to inform the analysis of clinical trial data and to guide the engineering of anti-Aβ antibodies with optimised specificity and affinity. We have determined the structures of three different AD antibodies in complex with Ab peptides: (1) WO2, which recognises the N-terminus of Aβ, (2) Mab 2286, which like the AD immunotherapeutic Ponezumab (Pfizer), shows specificity for the C-terminus of Aβ40 but has no significant cross-reactivity with Aβ42/43, and (3) Bapineuzumab, a humanized antibody developed by Pfizer and Johnson & Johnson which recognises the N-terminus of Aβ but cannot recognize N-terminally modified or truncated Aβ peptides (1). All these studies reveal surprising aspects of Aβ peptide recognition by the antibodies and suggest new avenues for AD antibody development.

[1] *1. Miles, L.A., Crespi, G.A.N., Doughty. L. & Parker, M.W. (2013) Bapineuzumab captures the N-terminus of the Alzheimer's disease amyloid-beta peptide in a helical conformation. Sci. Rep. 3, 1302*

Keywords: Alzheimer's disease, drug discovery, antibodies