DATE: Day 8 Month 5 Year 2017

SUMMARY of

2016 RESEARCH RESULTS REPORT

For International Collaborative Research with IPR, Osaka University

Research Title		Role of transient (fuzzy) interactions and dynamics in the interaction of an intrinsically disordered malaria vaccine candidate with the immune system
Applicant	**Name**	Raymond S. Norton
	Affiliation	Monash Institute of Pharmaceutical Sciences
	Present Title	Professor
Research Collaborator (Host PI)		Toshimichi Fujiwara (Professor)

Summary

Transient (weak) interactions play an essential role in regulating the dynamics of biological networks. However, it can be difficult to characterise such interactions experimentally, as they are generally highly dynamic. Nuclear magnetic resonance (NMR) spectroscopy is an excellent method for determining the structures of transient complexes and studying their dynamics. This study focuses on transient interactions that modulate the strain-specificity of a monoclonal antibody (6D8) binding to different allelic forms of a polymorphic malaria antigen, merozoite surface protein 2 (MSP2).

MSP2 is an intrinsically disordered protein consisting of conserved N- and C-terminal regions and a variable central region. Based on the variable sequences MSP2 is classified into two alleles, 3D7 and FC27. The 6D8 antibody recognizes a highly conserved continuous epitope within the N-terminal region of MSP2, comprised of residues 14-22. Despite binding to this well-defined epitope in a conserved region of the antigen, 6D8 has different affinities for the different allelic forms of MSP2. This suggests that 6D8 also makes interactions with residues that differ between 3D7 and FC27 MSP2.

Peptides which included the 6D8 epitope and extended into the variable region by 9 residues recapitulated this affinity difference, indicating that the variable-region residues that are close to the defined epitope are modulating their binding to 6D8. NMR chemical shift perturbation experiments were used to identify the 6D8 residues that interact with the MSP2 variable regions in these peptides. It was found that the perturbed residues in the spectra are distributed across a broad region of the 6D8 surface surrounding the paratope suggesting multiple conformations of the variable regions. The dynamics of the variable regions were studied by performing NMR relaxation experiments on the extended peptides bound to 6D8. The relaxation data confirm the transient nature of the interactions and highlight differences in extent or timescale due to the sequence-dependent conformational preferences of the peptides. The unexpected strain-specificity of the 6D8 antibody can be explained by differences in these transient interactions. The results from this work contribute to a broader understanding of the role of transient interactions in the binding of disordered antigens to their cognate antibodies.

***Deadline: May 19, 2017**
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