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"Heterobifunctional ligand-driven self assembly of multivalent IgM-CD22 complexes on B cells"

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Abstract:

Glycan binding proteins are widely employed in the immune system for such events as pathogen recognition, cellular trafficking, and regulation of the immune response. Protein-carbohydrate interactions are typically of low affinity, and therefore multivalency is a common mechanism for engagement. One family of such proteins comprises the sialic acid-binding immunoglobulin-like lectins, or Siglecs. Siglec-2 (CD22) is an endocytic receptor expressed only on B cells, making it a target for immunotherapy of B cell malignancies. The native function of CD22 is to regulate the B cell receptor *via* intracellular signalling motifs. Synthetic multivalent sialoside ligands have been developed as tools to study the biology and therapeutic targeting of CD22.

A heterobifunctional ligand was designed that incorporates a high-affinity sialoside ligand for CD22 and the hapten, nitrophenol (NP), which is recognized by the decavalent antibody, anti-NP IgM. Ligands are able to drive the self-assembly of IgM-CD22 complexes at the surface of the native B cell, competing with the masking effect of highly abundant CD22 ligands present on the B cell surface (*cis* ligands). Rapid accumulation of intracellular ligand suggested that CD22 is a recycling receptor. To prove this, a reversible biotin-tagging strategy was employed. Preliminary studies suggest that the multivalent ligand may alter the intracellular fate of CD22. A tetravalent anti-NP IgA can more sensitively discriminate the degree of CD22 masking by *cis* ligands on the B cell surface, suggesting that ligands with intermediate valency may selectively target glycan-binding proteins with greater functional availability.