Cracking the sugar code: New tools and techniques to study glycan-protein binding interactions

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All cells are decorated with complex carbohydrate structures called glycans. Glycan-binding proteins interact with glycans to mediate many biological processes, such as immune regulation and inflammation. Despite their abundance and importance, the functions of specific glycan structures remain poorly understood. Mapping the functions and interactions of glycans with their protein binding partners is key to advancing an understanding of human health and disease. However, the structural complexity of glycans, low binding affinities of glycan-protein binding interactions, and a lack of accessible tools to synthesize glycans to study glycan-protein interactions have hindered glycobiology research.

Our group has been leveraging glycosyltransferases, enzymes that form glycosidic bonds during glycan biosynthesis, to address the challenges in accessing structurally defined glycan probes. Chemoenzymatic methods leverage the regio- and stereospecificity of glycosyltransferases to access glycans decorated with a variety of terminal glyco-epitopes, incorporating both natural and bioorthogonally functionalized monosaccharides. The combination of chemical and enzymatic synthesis drastically reduces step count and streamlines access to these probes compared to chemical synthesis alone. In this presentation, we will discuss our chemoenzymatic strategy to prepare a library of sialylated O-glycan probes and highlight their applications in characterizing the glycan ligand preference of Siglec-7, an immune receptor protein implicated in how cancer cells evade immune surveillance. These chemical glycobiology tools provide new avenues to interrogate glycan-protein binding interactions, allowing us to crack the sugar code and develop new glycan-based therapeutics to benefit human health.