THE UNIVERSITY OF TOLEDO
1872

Department of Chemistry
Colloquium Speaker

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"Synthesis and Biological Studies of GPI Anchors and GPI-Anchored Proteins"

Many surface proteins and glycoproteins are anchored to the cell membrane via glycosylphosphatidyl- inositols (GPIs), a group of complex glycolipids sharing a conserved core structure: H_2N-CH_2CH_2-OPO_3-6-α-Man-(1→2)-α-Man-(1→6)-α-Man-(1→4)-α-GlcNH_2(1→6)-inositol-1-OPO_3-glycerolipid. All GPI-anchored proteins and glycoproteins have their polypeptide *C*-termini linked to the conserved phospho-ethanolamine moiety. GPI-anchored proteins and glycoproteins play a critical role in various biological and pathological events. To study these events, it is essential to have access to GPIs and GPI-anchored proteins and glycoproteins in homogeneous and structurally well-defined forms, which is a significant challenge. Our research aims at developing methodologies for the synthesis of natural and functionalized GPI anchors and GPI-peptide, glycopeptide, protein and glycoprotein conjugates, as well as studying GPI biology using synthetic GPIs and GPI conjugates.

We have developed a highly convergent strategy for GPI anchor synthesis utilizing a phospholipidated pseudodisaccharide as the common key intermediate, and applied it to the preparation of many GPIs and GPI analogues. With *p*-methoxybenzyl group as a permanent protection of hydroxyl groups, the strategy was also used to prepare GPIs with unsaturated lipids and other functionalities. We have also developed chemical and enzymatic methods for the synthesis of structurally well-defined GPI-linked peptides and proteins. For the enzymatic synthesis, free GPI anchors and peptides, glycopeptides and proteins were effectively ligated with sortase A, a transpeptidase utilized by bacteria to link surface proteins to the cell wall. We have demonstrated that sortase A could accept GPIs having one or multiple glycine residues attached to the conserved phosphoethanolamine moiety as substrates and couple them with peptides, glycopeptides or proteins. Sortase A was also used to prepare macrocyclic peptides and glycopeptides or attach proteins to liposomes. The synthetic GPIs, functionalized GPIs, and various GPI conjugates have been used to study how bacterial toxins interact with GPIs and how GPIs distribute in membranes, and to study the structure-activity relationships of GPIs and cell surface GPIomics.

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