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Structure based design of novel glycosyl transferases used for site-specific antibody-drug conjugation via glycan chains

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Molecular cloning and structure-function studies on the Golgi-glycosyltransferases (GTs) and lactose synthase enzyme, a complex between beta-1,4-galactosyltransferase (b4-Gal-T1) and a protein alpha-lactalbumin (LA) that modulates the activity of b4-Gal-T1, has revealed that GTs have flexible loops. Upon binding of the sugar donor substrate the flexible loops of GT undergo a marked conformational change from an open to a closed conformation, repositioning the amino acid residues to lock the sugar donor ligand in place. This conformational change, in which the loop acts as a lid covering the bound donor substrate, creates an acceptor-binding site and the binding site for LA in the case of lactose synthase enzyme. After the glycosyl-unit is transferred from the sugar donor to the acceptor, the saccharide product is ejected and the loop reverts to its native conformation thereby releasing the remaining nucleotide moiety. Generally the specificity of the sugar donor is determined by few residues in the sugar-nucleotide binding pocket of the GT which are conserved among the family members from different species. The mutation of these residues has allowed us to design new and novel glycosyltransferases which can transfer donor sugar with a chemical handle that have vast applications for the bioconjugation of drugs to antibodies via glycan chains and the detection of glycans on cell surface. The therapeutic cargo molecules conjugated to the glycan moiety of a monoclonal antibody generating antibody-drug conjugates (ADCs), are becoming powerful therapeutic tools for cancer treatment.

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