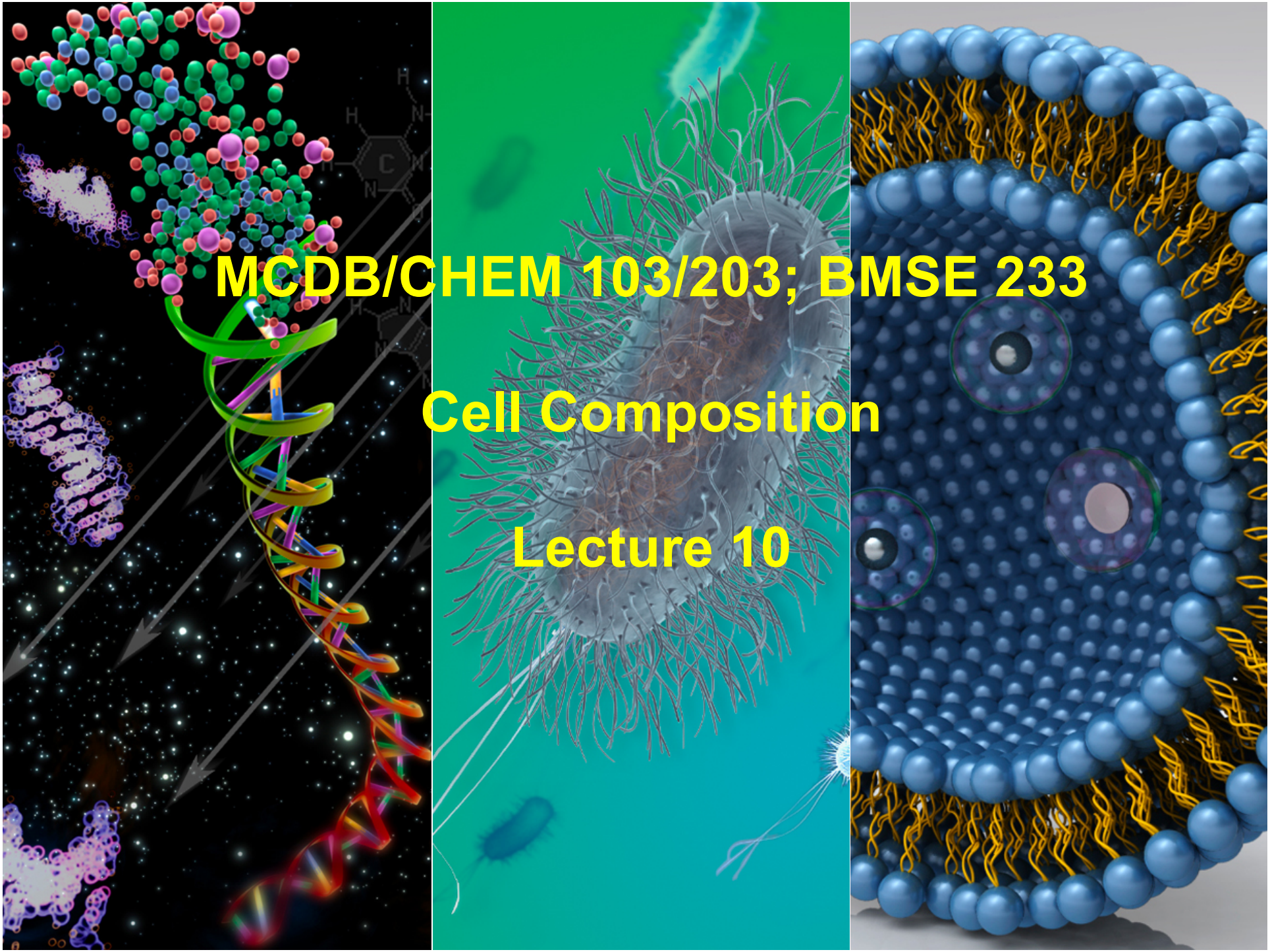
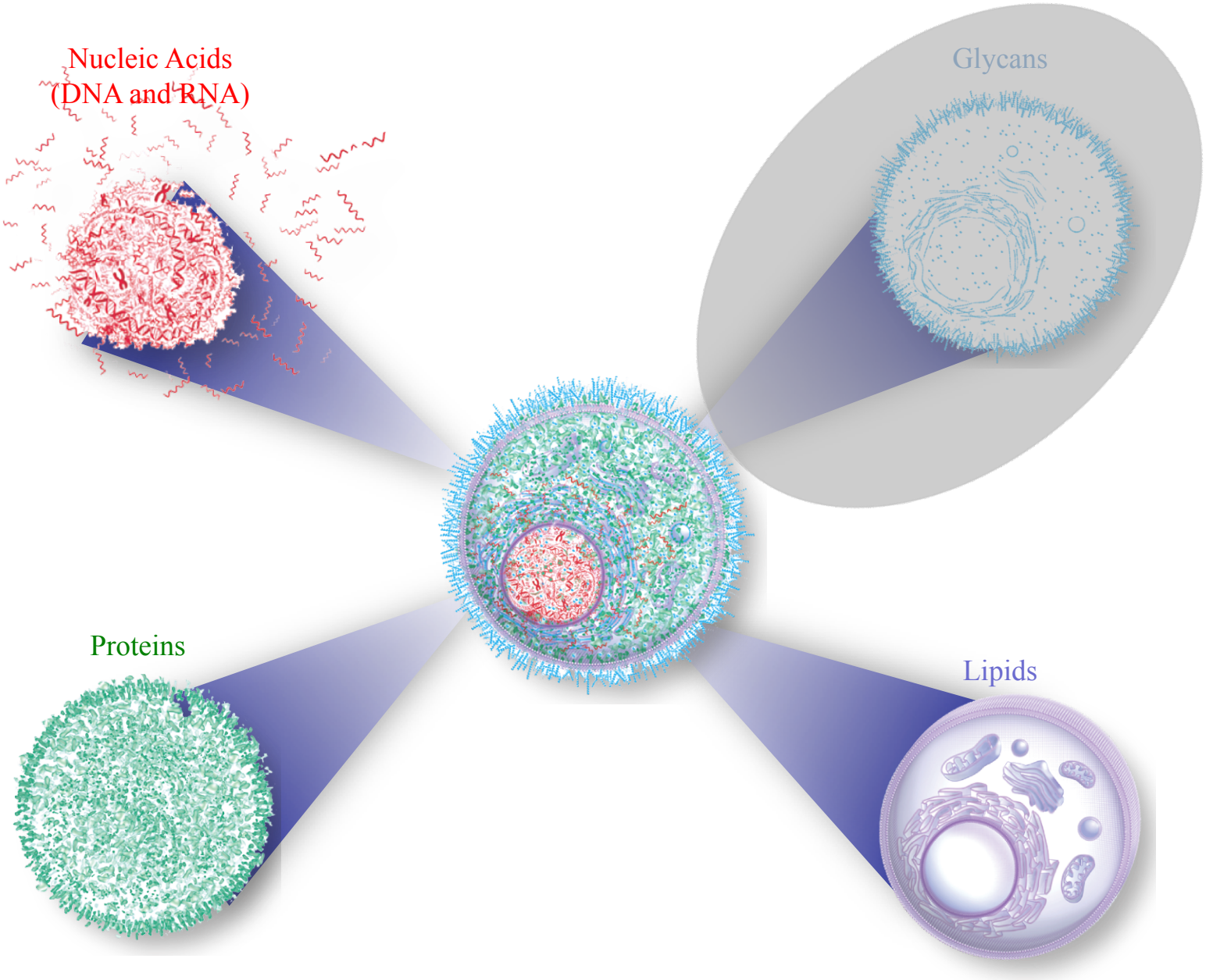


MCDB/CHEM 103/203; BMSE 233

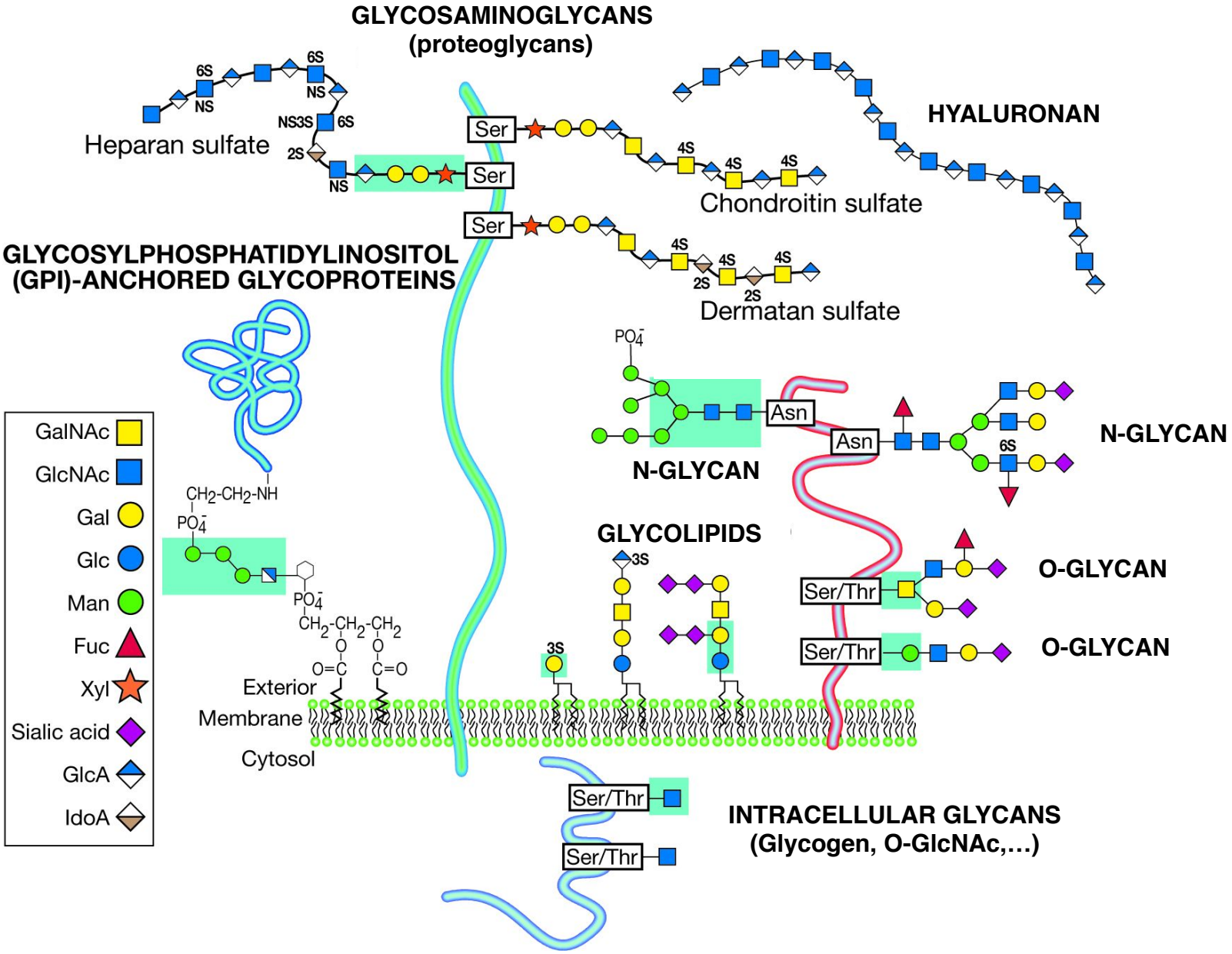
Cell Composition

Lecture 10

Cells are Composed of Four Types of Molecular Components



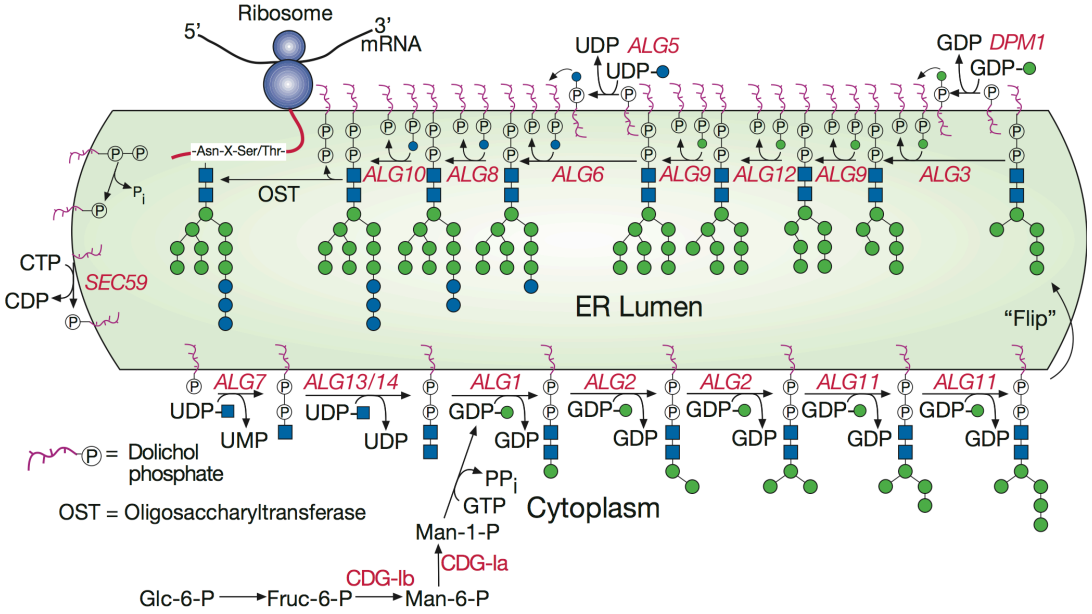
Common Classes of Vertebrate Glycans



Glycans:

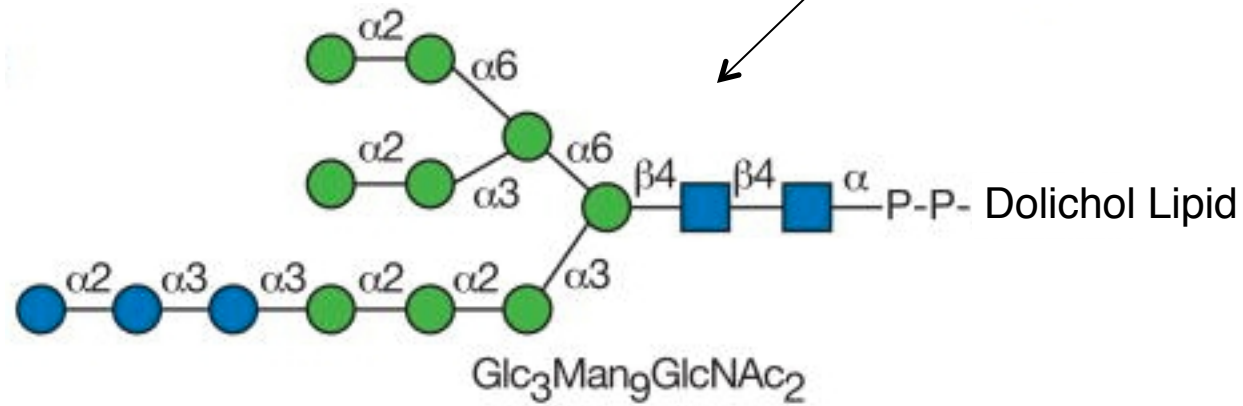
N-Glycans

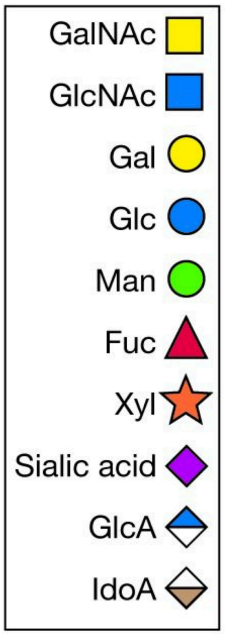
Synthesize of the Dolichol-PyrophosphateGlcNAc$_2$Man$_9$Glc$_3$ Precursor Used to Initiate N-Glycosylation (in All Eukaryotic Cells)



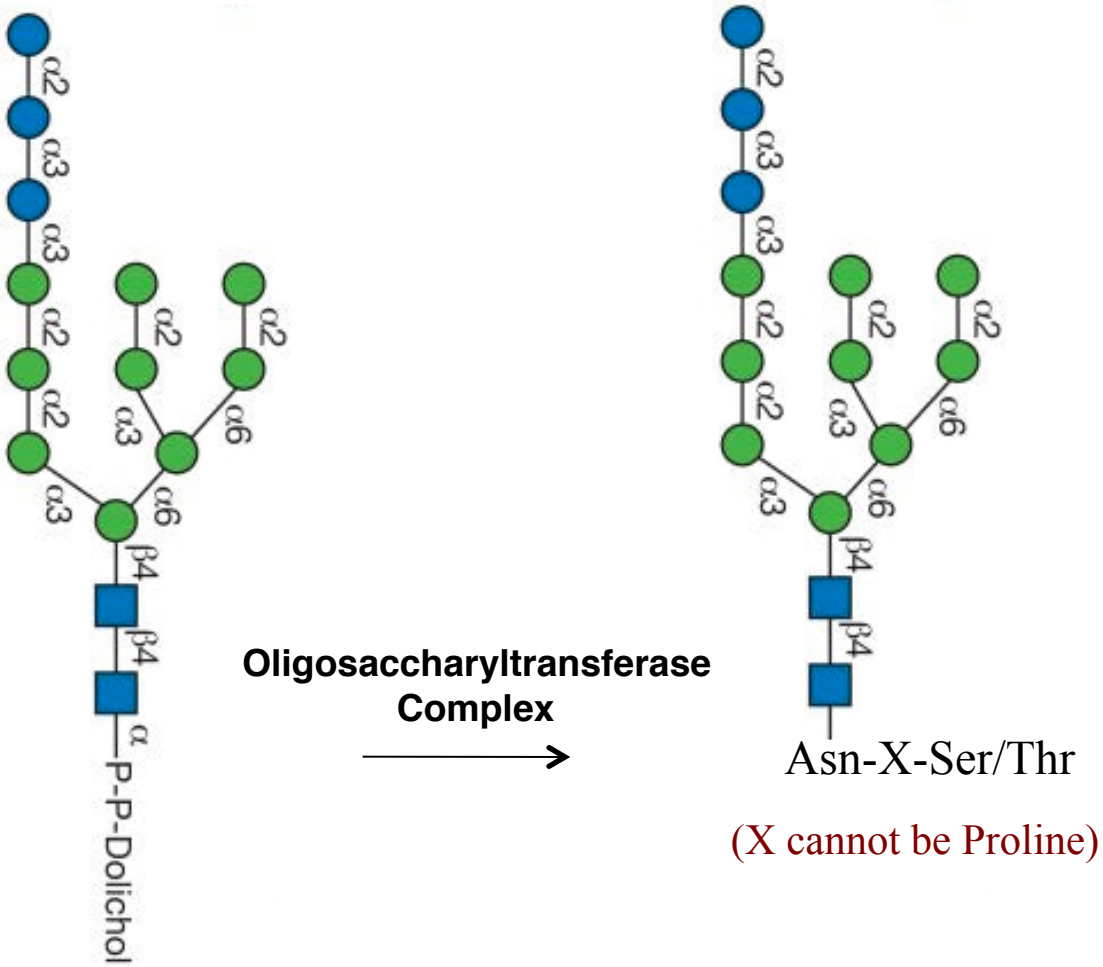
Many Steps are Required

This, to make this





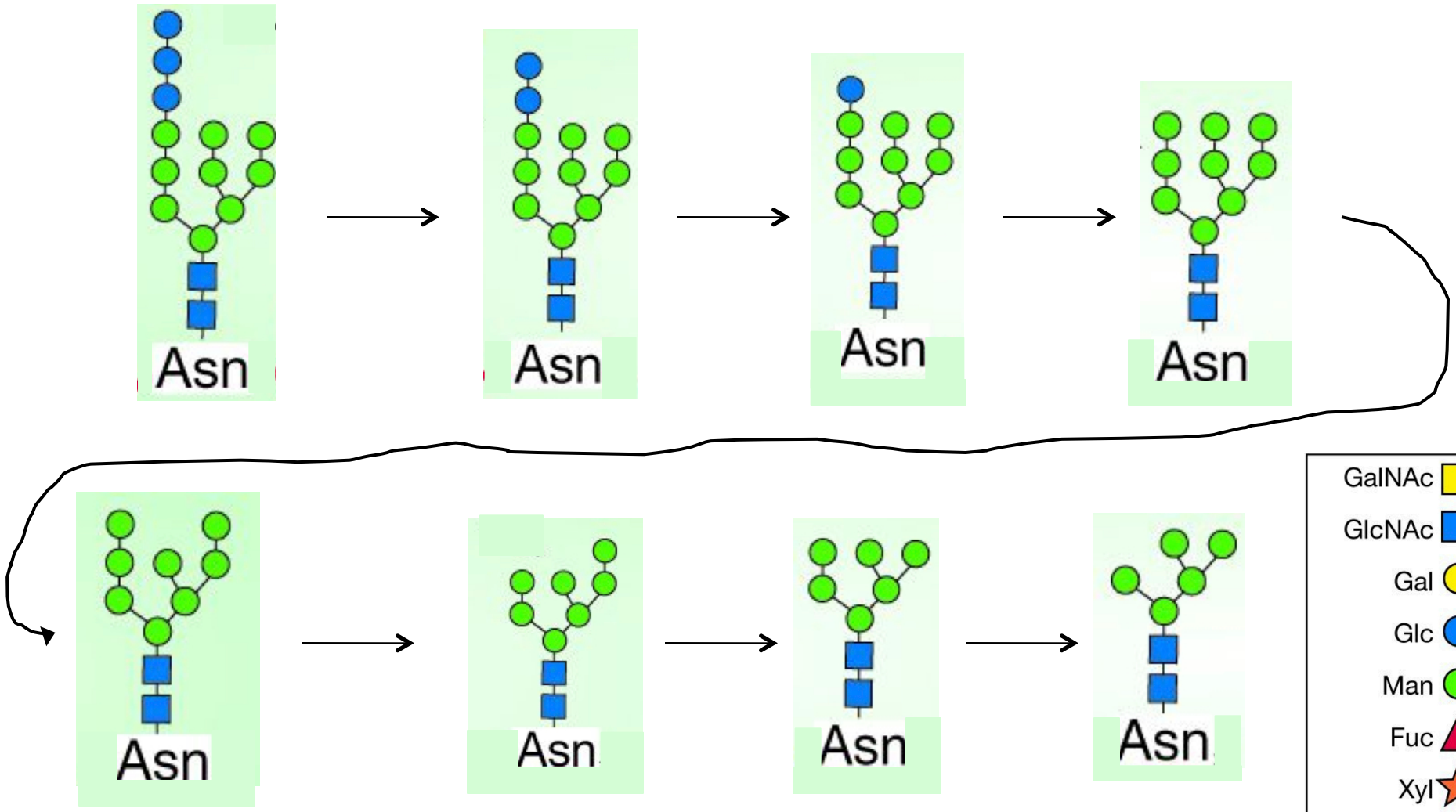
N-Glycosylation Requires the Oligosaccharyltransferase Complex and an Amino Acid Consensus Sequence in Proteins



N-Glycans occur on asparaginesin the Asn-X-Ser/Thr sequon of many secreted and membrane-bound glycoproteins. Analyses of protein sequence databases have revealed that about two thirds of the entries contain one or more Asn-X-Ser/Thr sequence. It is estimated that at least two thirds of those sequons are N-glycosylated. Occasionally, N-glycans are found on the Asn of the Asn-X-Cys motif, provided that the cysteine is in the reduced form. Although there have been several published reports of nucleocytoplasmic or cytoplasmic N-glycans, there exists at present no definitive evidence that N-glycans occur on cytoplasmic or nuclear proteins nor on the cytoplasmic portions of membrane proteins.

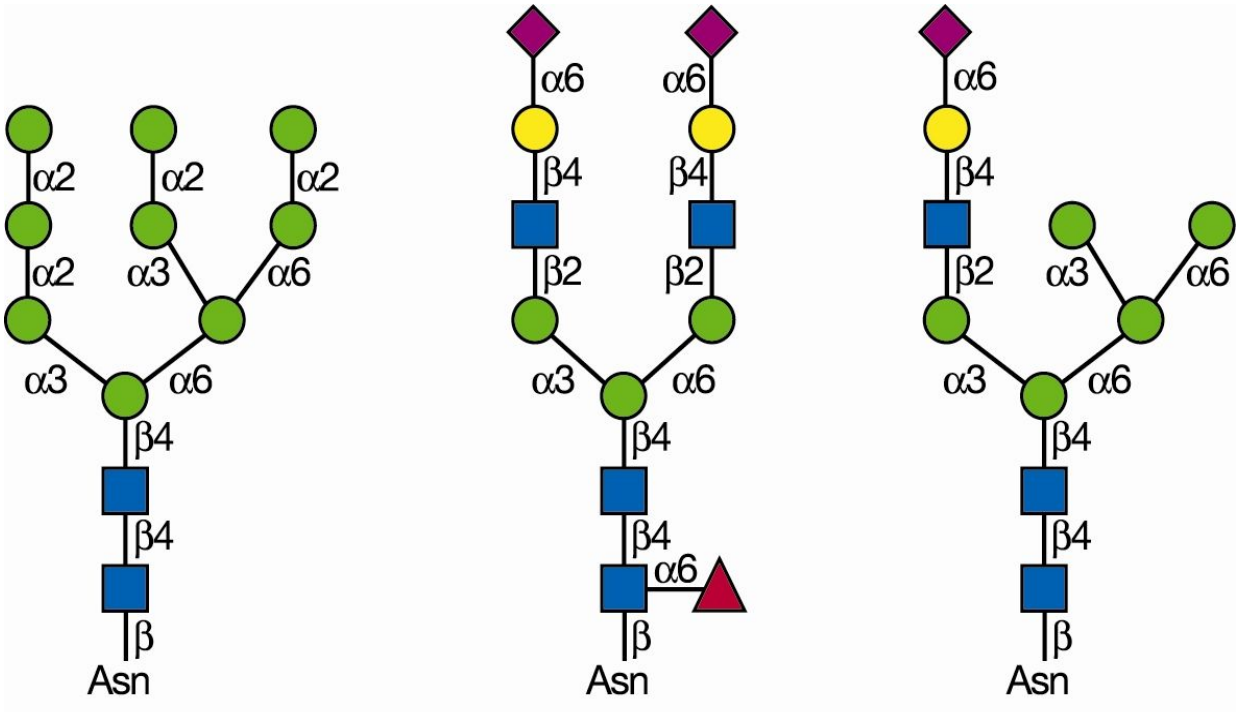
Initial N-Glycan Processing in Vertebrates

($Glc_3Man_9GlcNAc_2$ ⟶ Man_5GlnAc_2)



N-glycans are trimmed down to mannose types by mannosidases before they Become built up and elaborated. This trimming is important during protein folding (we will see this later in the course).

Common Types of Vertebrate N-Glycans

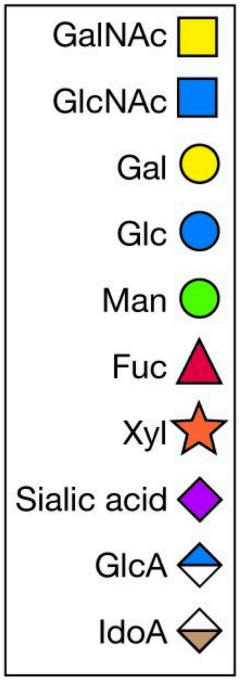


High-Mannose or Oligomannose

Complex

Hybrid

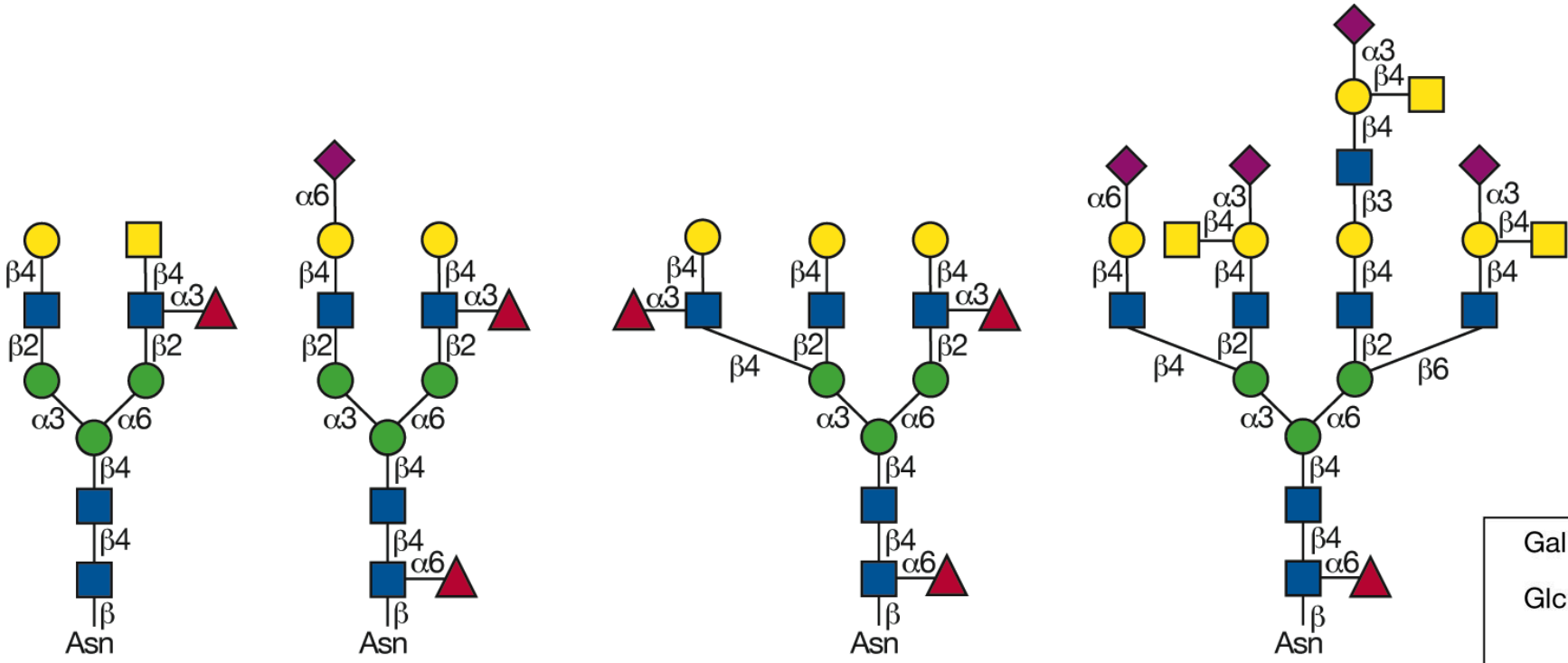
N-glycans are branched structures



Classification is based on mannose presence in termini of branched N-glycans

Cell surface and extracellular N-glycans produced by vertebrate cells are predominantly of the Complex type. Relatively few are of the High-Mannose/Oligomannose type.
No evidence exists that vertebrate cells normally produce hybrid N-glycans other than as biosynthetic intermediates between mannose and complex forms.

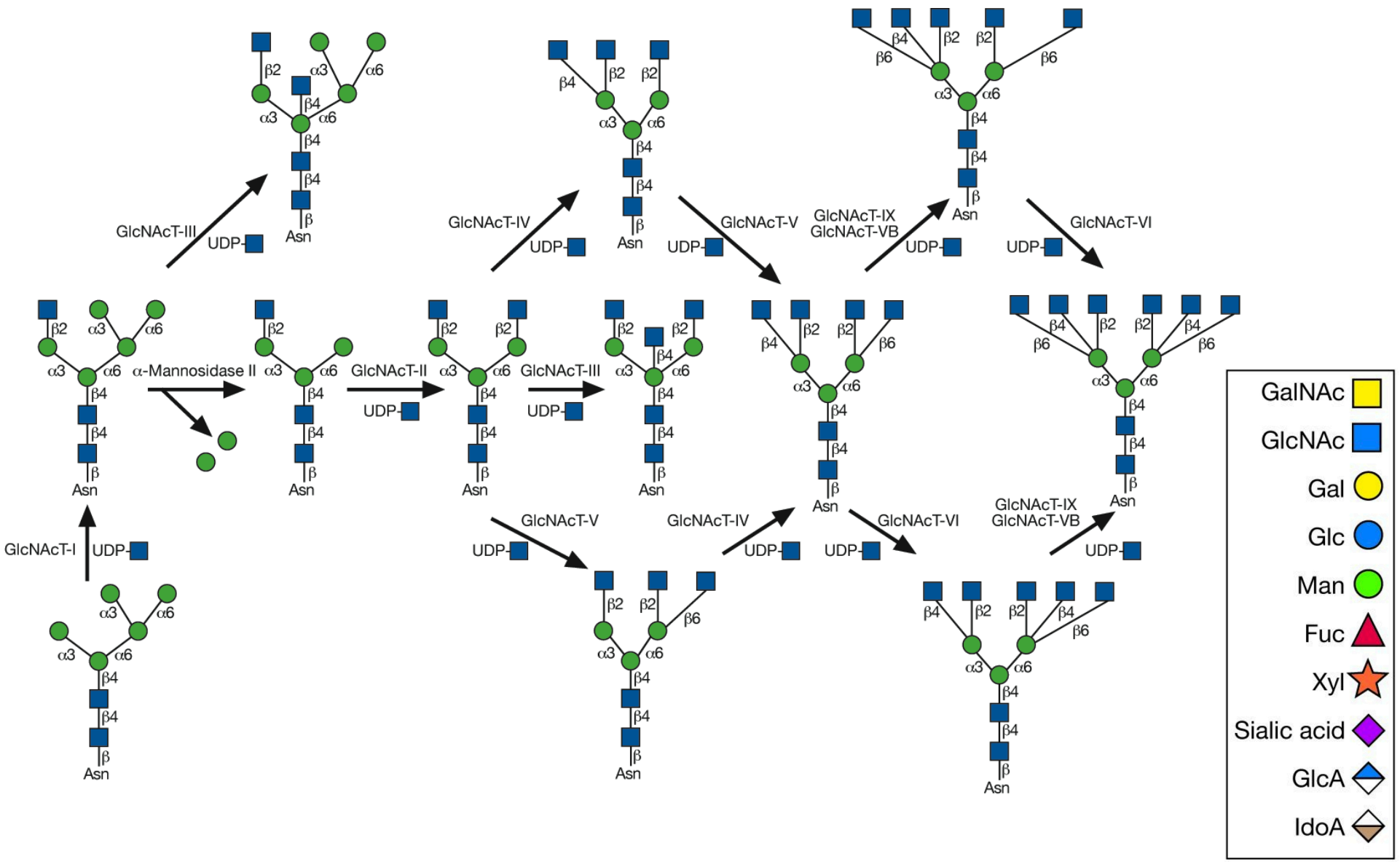
Multiple Examples of Complex N-Glycans Attached to Various Glycoproteins: Multiple Branched Structures



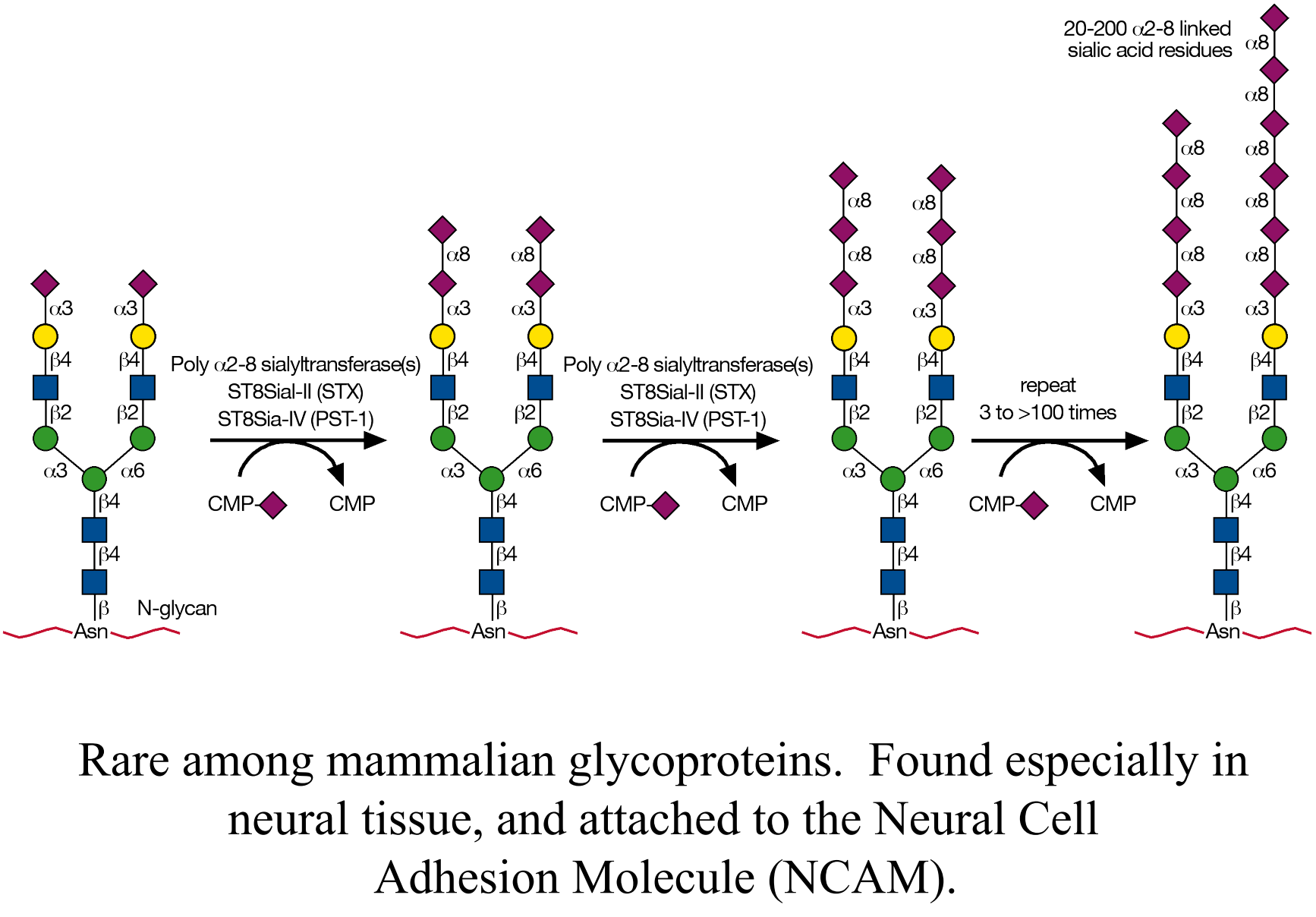
Bi-antennary **Tri-antennary** **Tetra-antennary**

Most branches are terminated with sialic acids, some with galactose. GlcNAc termini are rare in mammals, but more common in lower vertebrates.

Sequential Processing by Glycosyltransferases and Glycosidases Can Produce Different Branched Structures: Not All of the Possible Branched Forms Shown Below Have Been Found

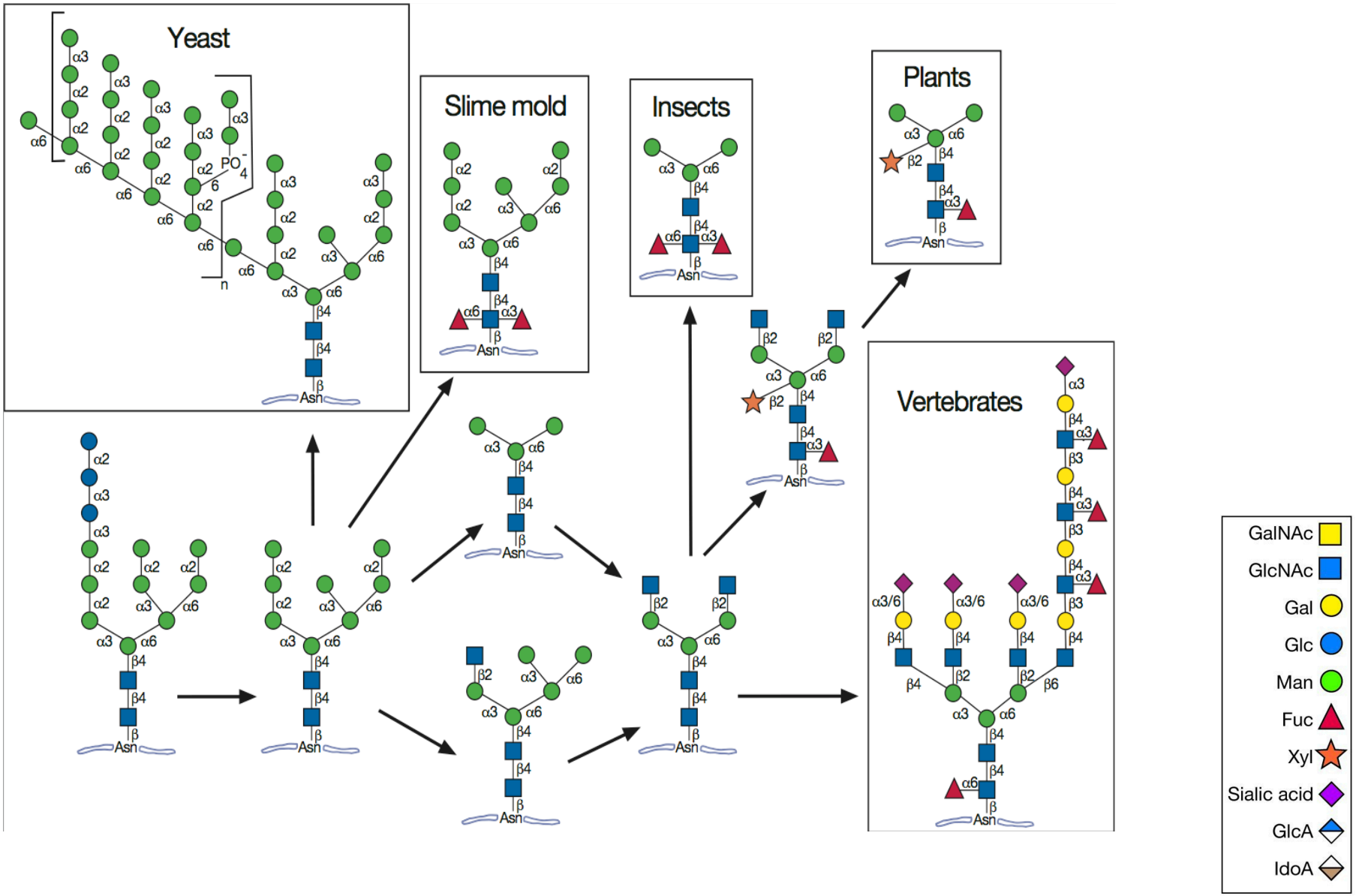


Synthesis and Structure of Polysialic Acid on N-Glycans

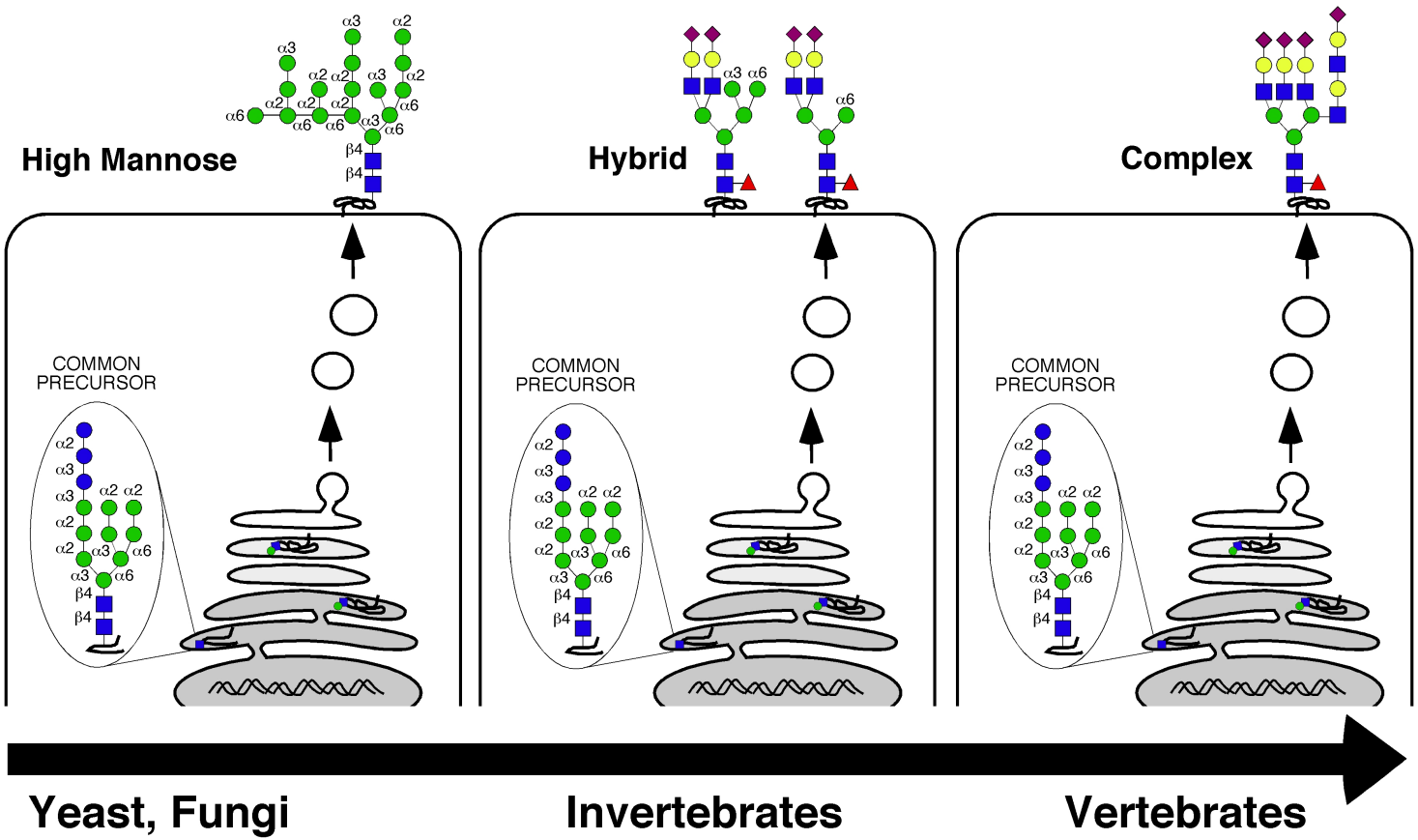


Rare among mammalian glycoproteins. Found especially in neural tissue, and attached to the Neural Cell Adhesion Molecule (NCAM).

Dominant Pathways of N-Glycan Maturation Among Different Organisms



Cell Surface and Extracellular N-Glycans in Phylogeny



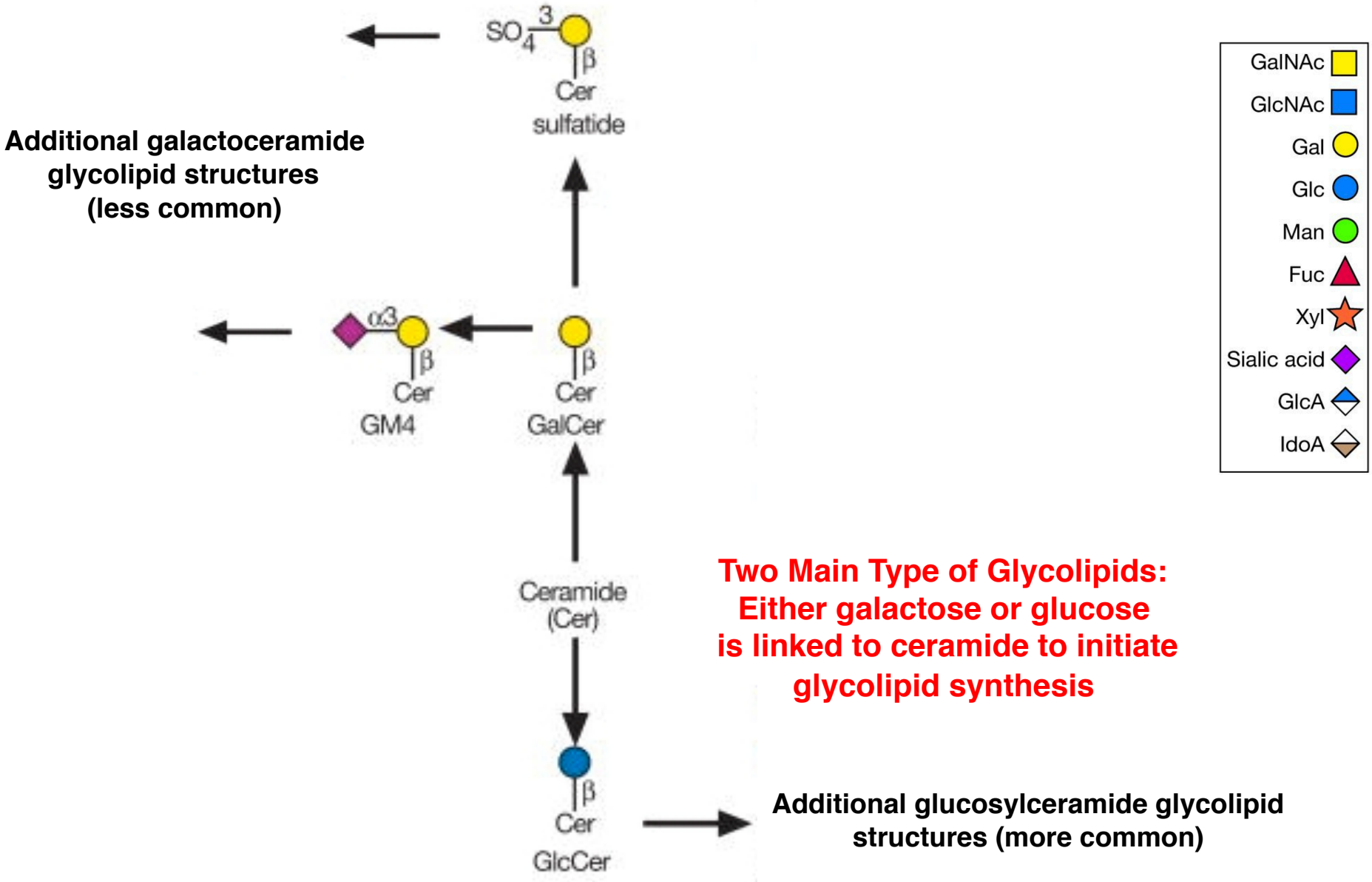
The phylogenic differences in mature N-glycans are detected by the innate immune system of vertebrates. This can result in inflammation, and may contribute to mechanisms of human autoimmune and degenerative diseases

Glycans:

Saccharolipids / Glycolipids

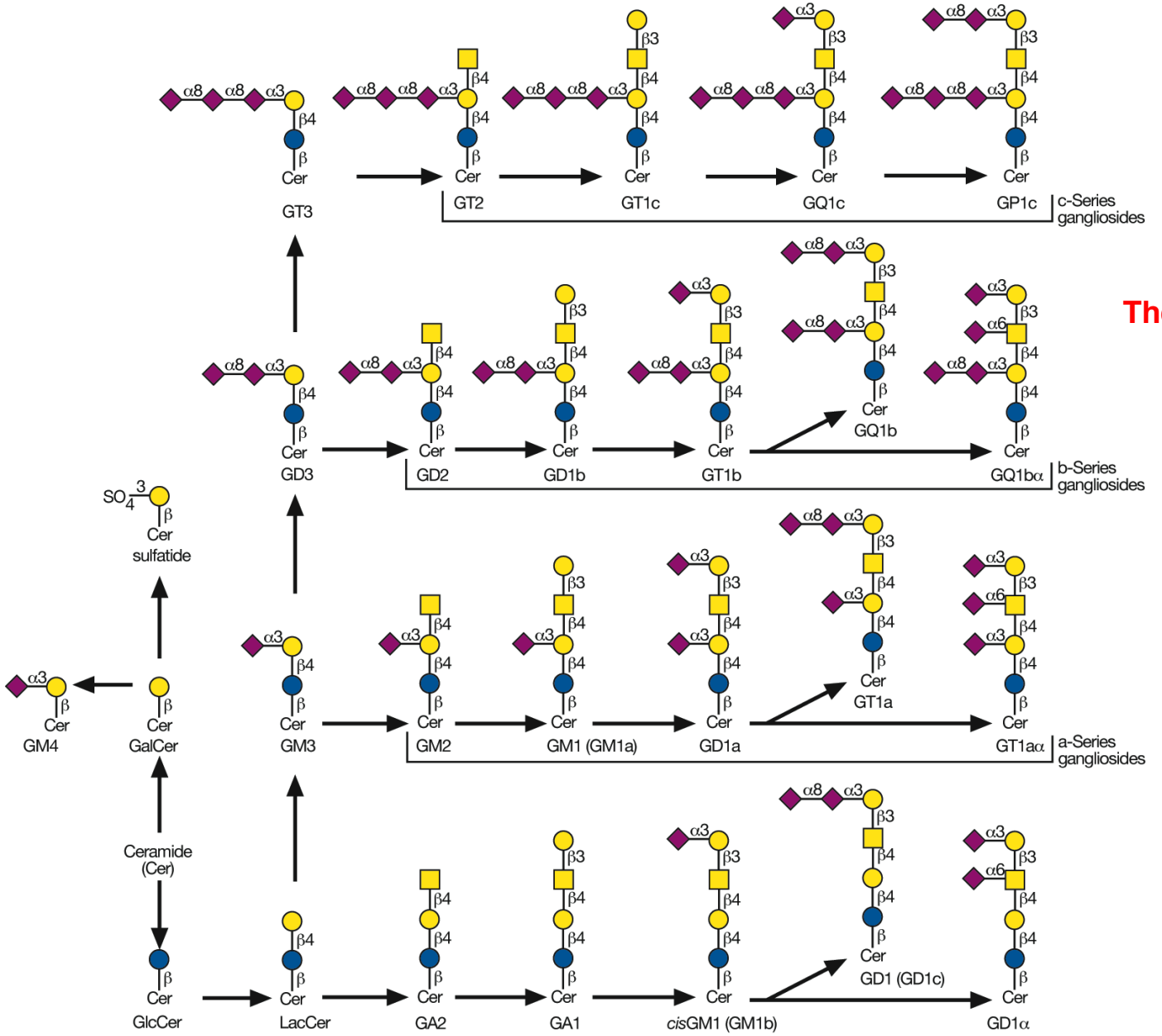
Ceramide : A Common Type of Lipid Found in Membranes and a Building Block of Glycolipids/Saccharolipids

Glycolipid/Saccharolipid Biosynthesis: First Steps



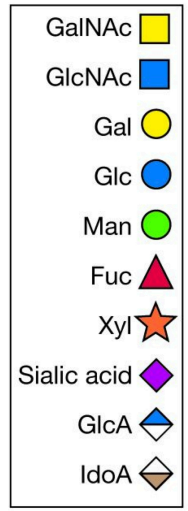
Two Main Type of Glycolipids: Either galactose or glucose is linked to ceramide to initiate glycolipid synthesis

Glycolipid/Saccharolipid Biosynthetic Pathways



These glycosphingolipids are common in brain tissue

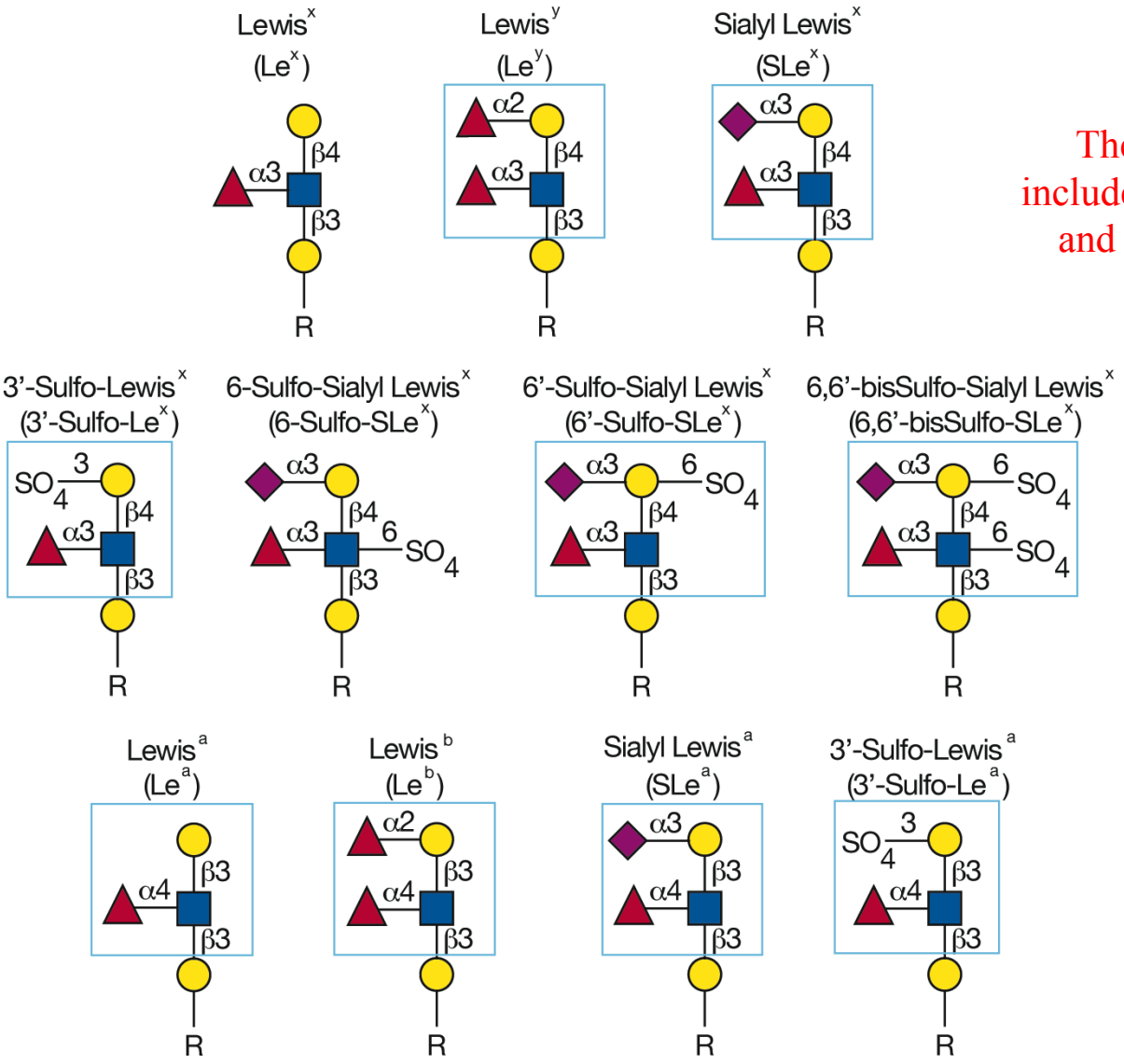
Note some contain polysialic acid



Glycans:

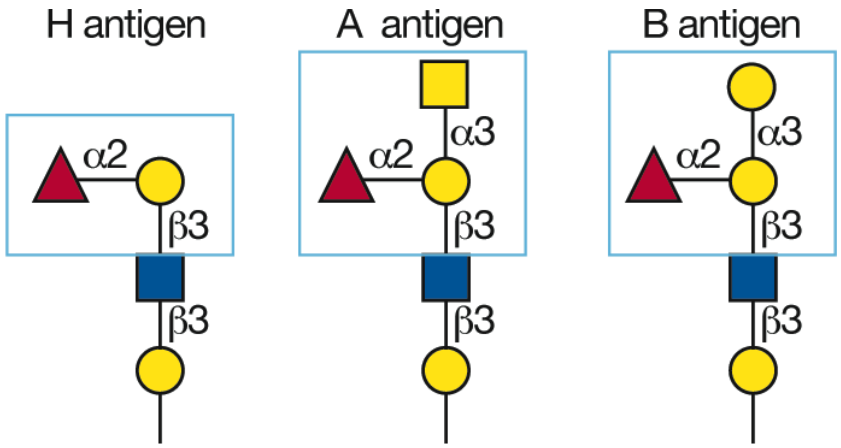
Examples of Common Glycan Branch Termini Found on Different Glycan Classes

The Lewis Series of Glycan Antigen Determinants are Found on O-Glycans, N-glycans, and Glycolipids



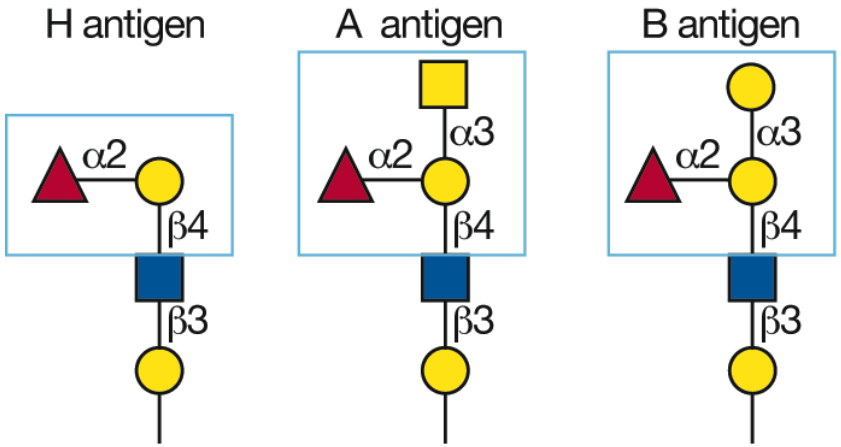
The Lewis antigens include cell differentiation and stem cell markers

Glycans that Form the O (H), A, and B Blood Group Antigens on the Termini of N- and O-Glycan Chains

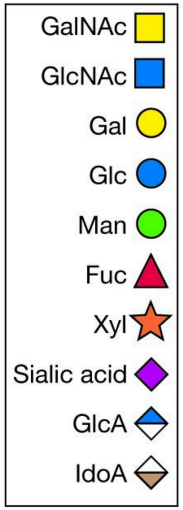


Type 1 chain termini

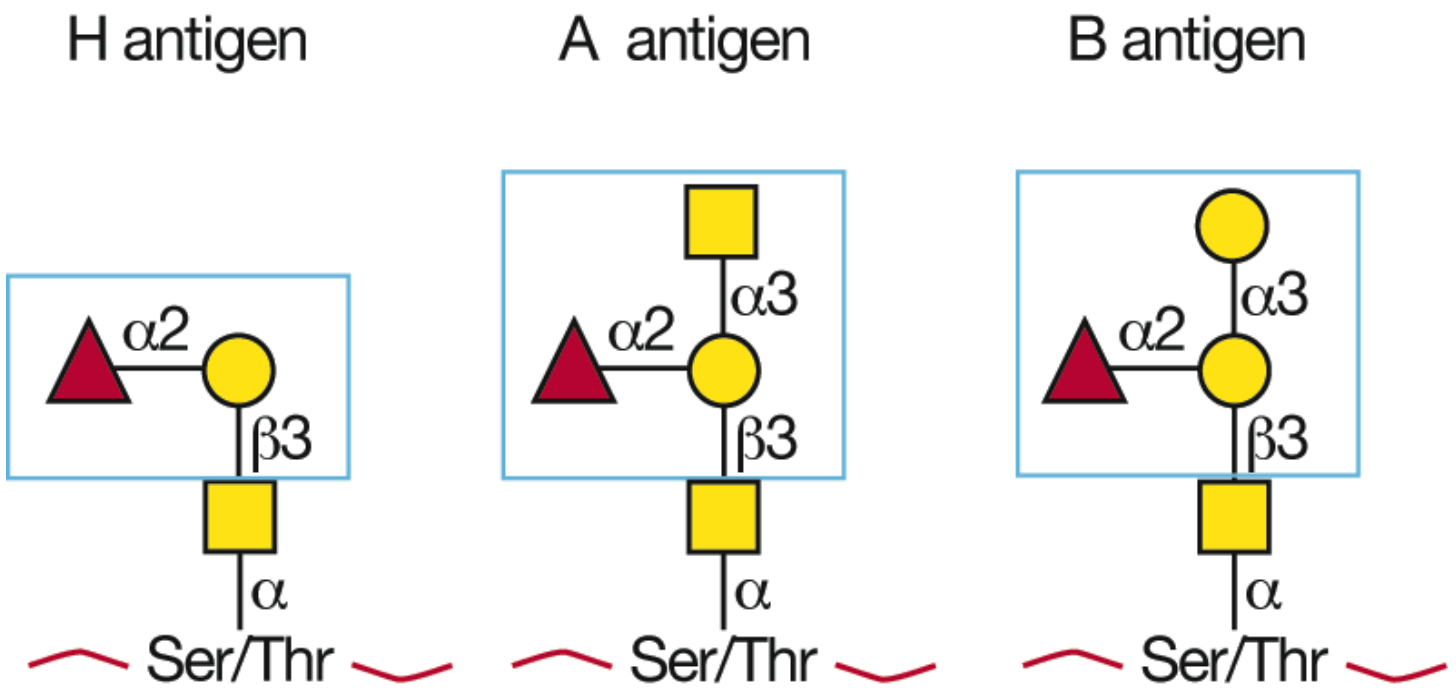
The anomeric linkage state of Gal to GlcNAc defines the different Type of chains

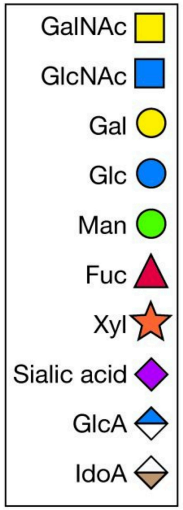


Type 2 chain termini



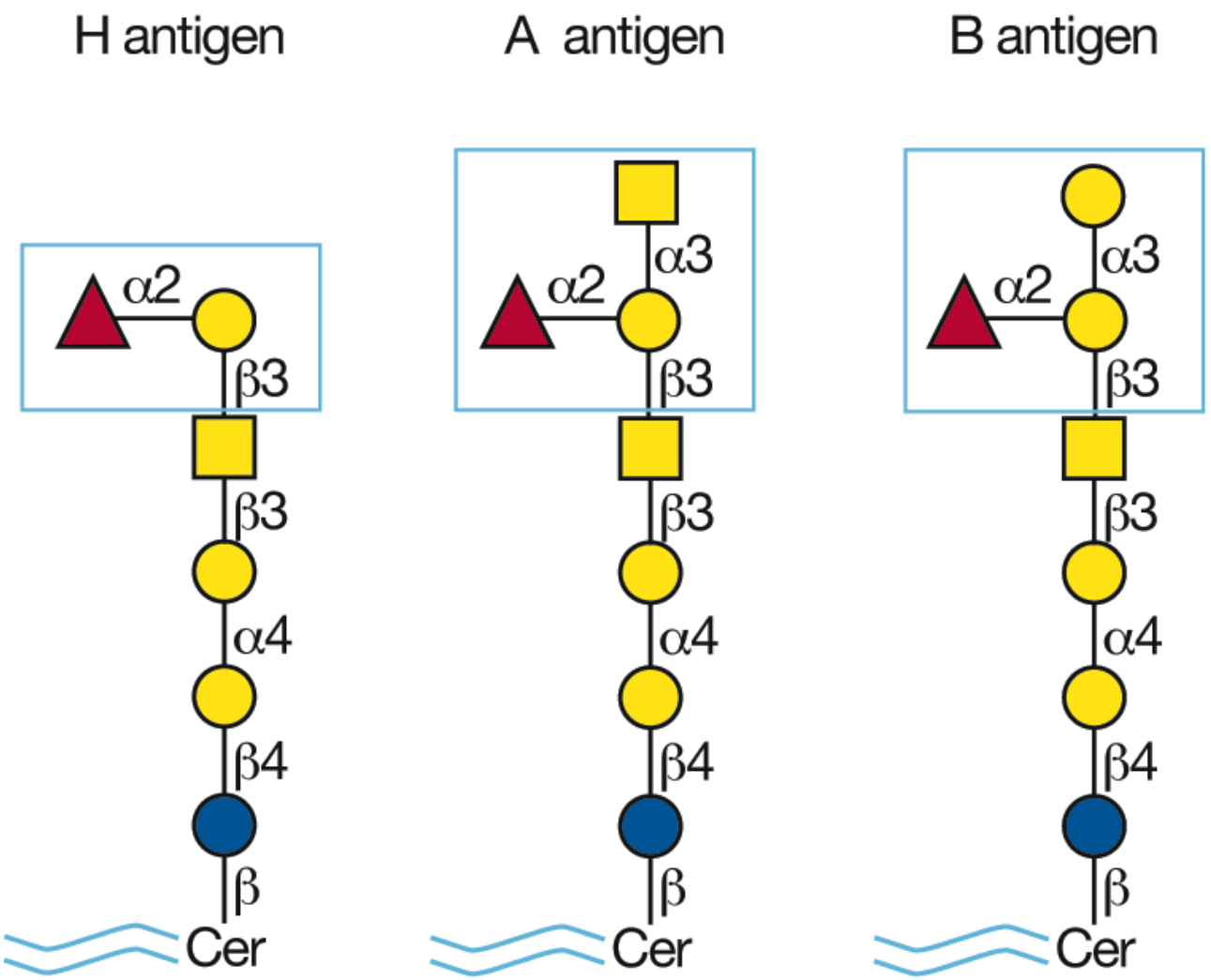
The O (H), A, and B Blood Group Antigens Can Also be Found on Short O-Glycan Chains





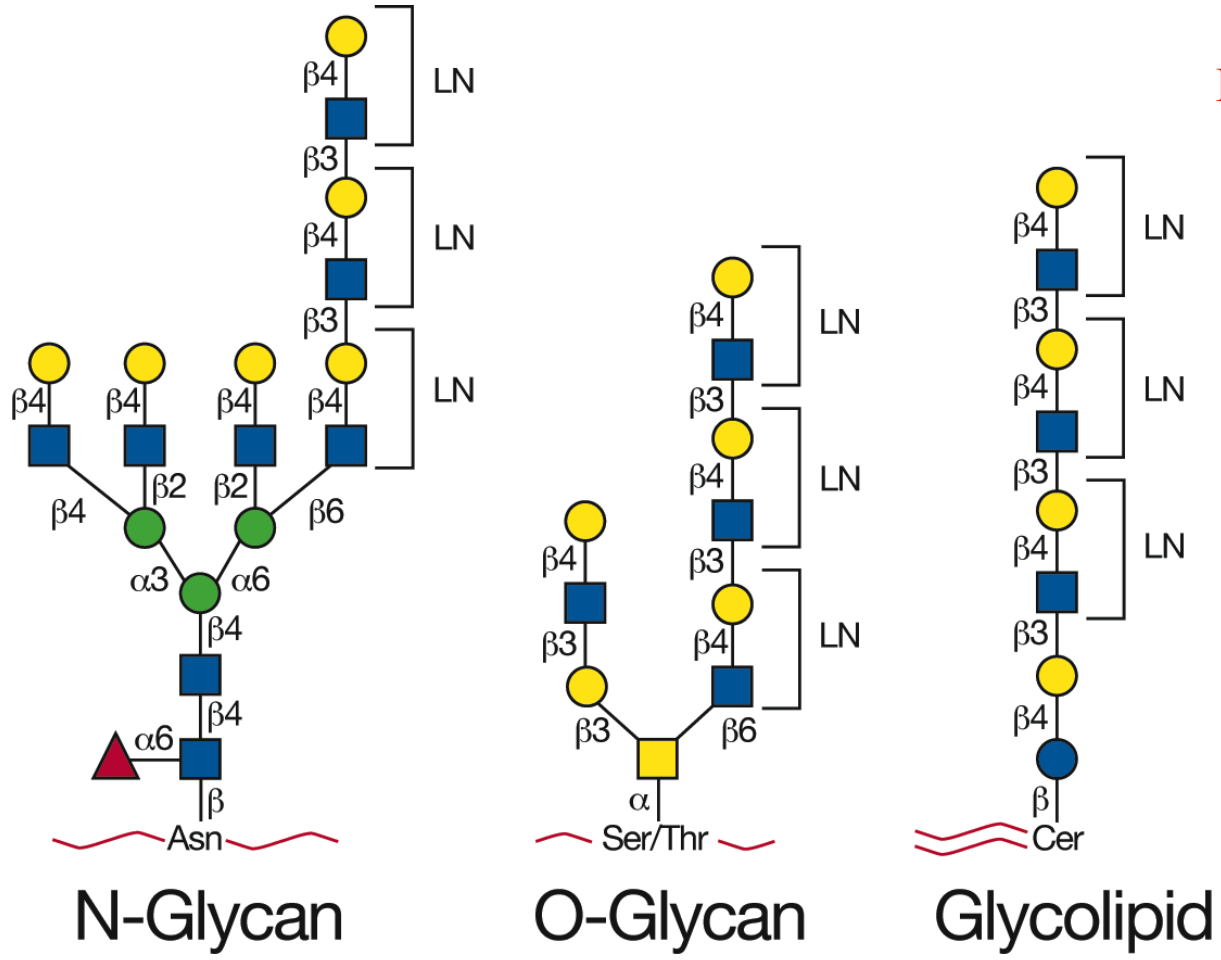
What type of Core O-glycans are these?

Glycans that Form the O (H), A, and B Blood Group Determinants on Glycolipids



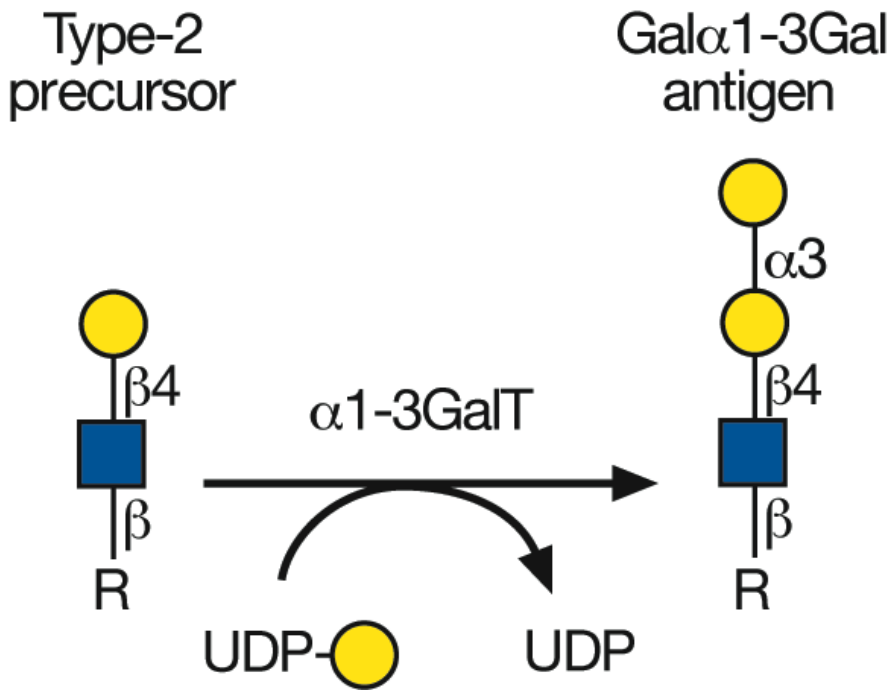
Cer = ceramide

Poly-*N*-Acetyllactosamine Chains are Found on N-Glycans, O-Glycans, and Glycolipids

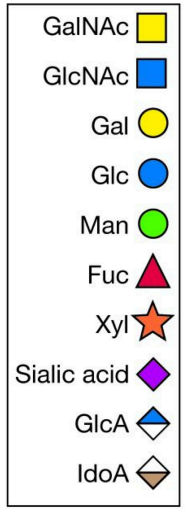


Polylactosamines are increased among glycans from cancer cells.

Synthesis of the Galα1-3Gal Glycan Terminus of Glycan Chains: The Major Xenotransplantation Organ Rejection Antigen



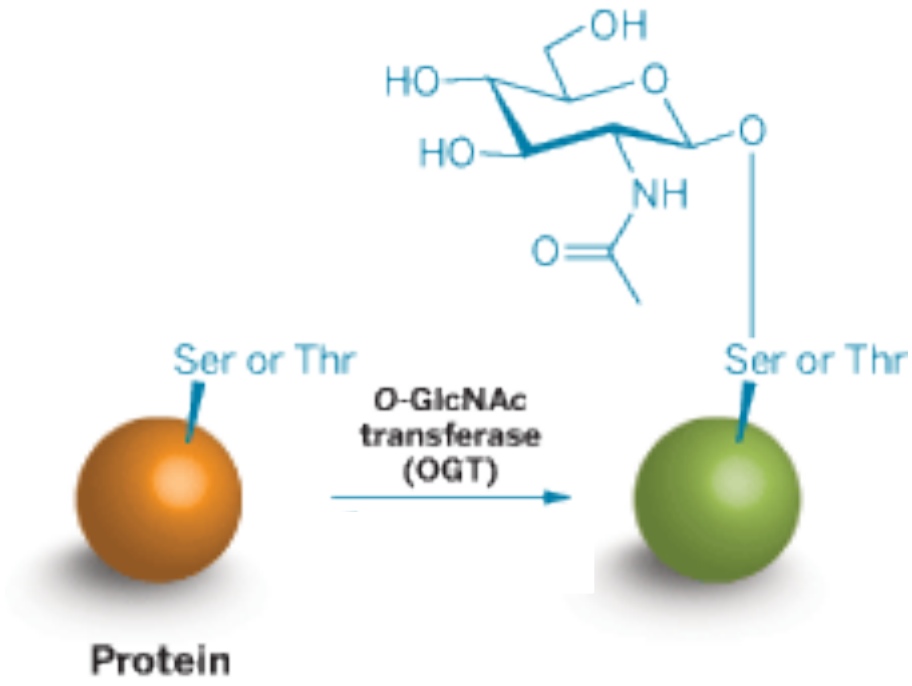
Old World Primates (us) all lack α1-3 galactose linkages in our glycans because of null mutations in the genome that inactivate the gene encoding the α1-3 galactose transferase.



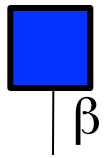
Glycans:

The Intracellular O-GlcNAc Modification

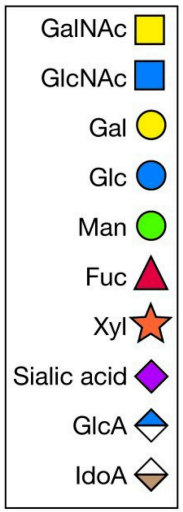
The O-GlcNAc Glycan linkage is Found in the Cytoplasm and Nucleus of Multicellular Organisms



O-GlcNAc

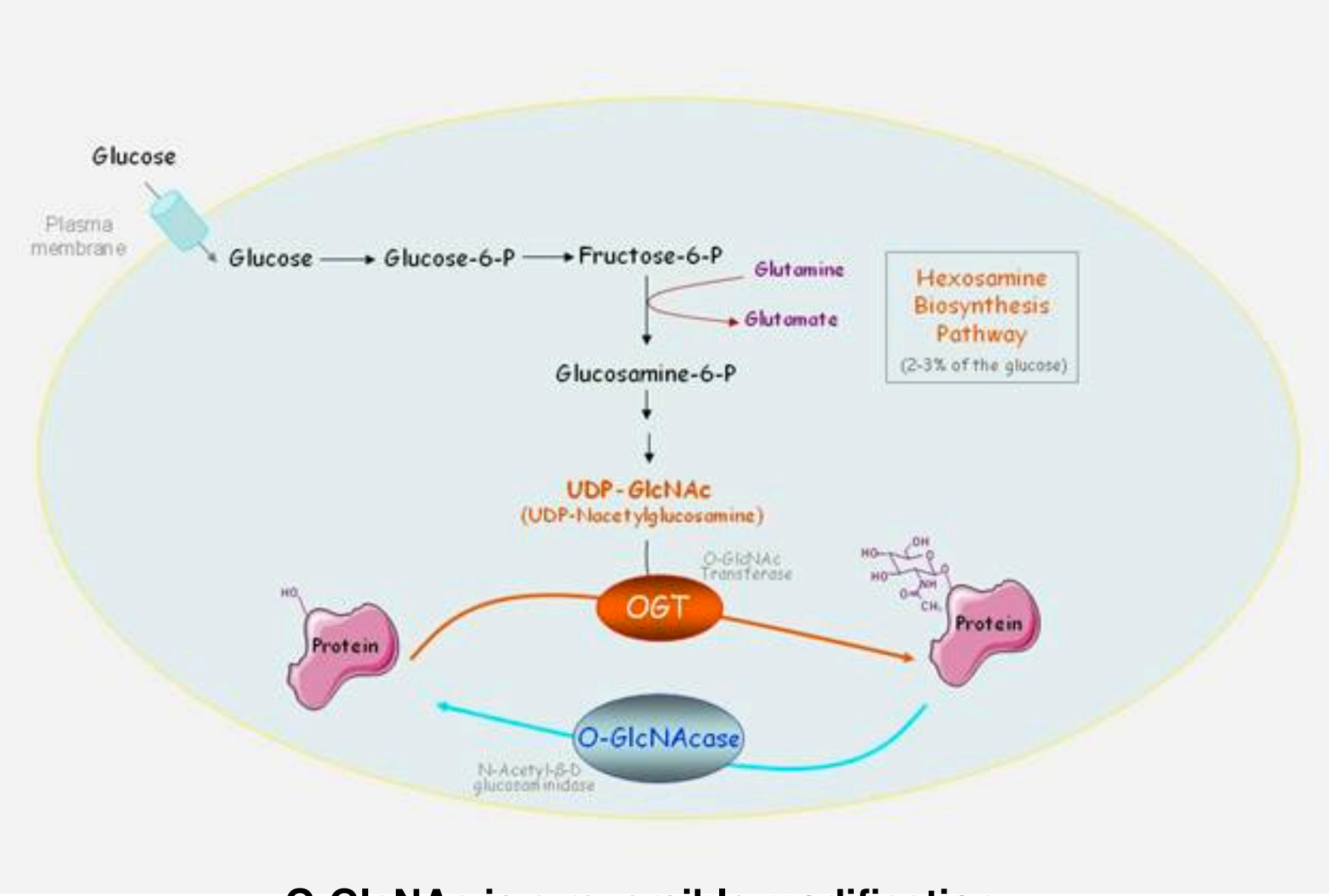


Ser/Thr



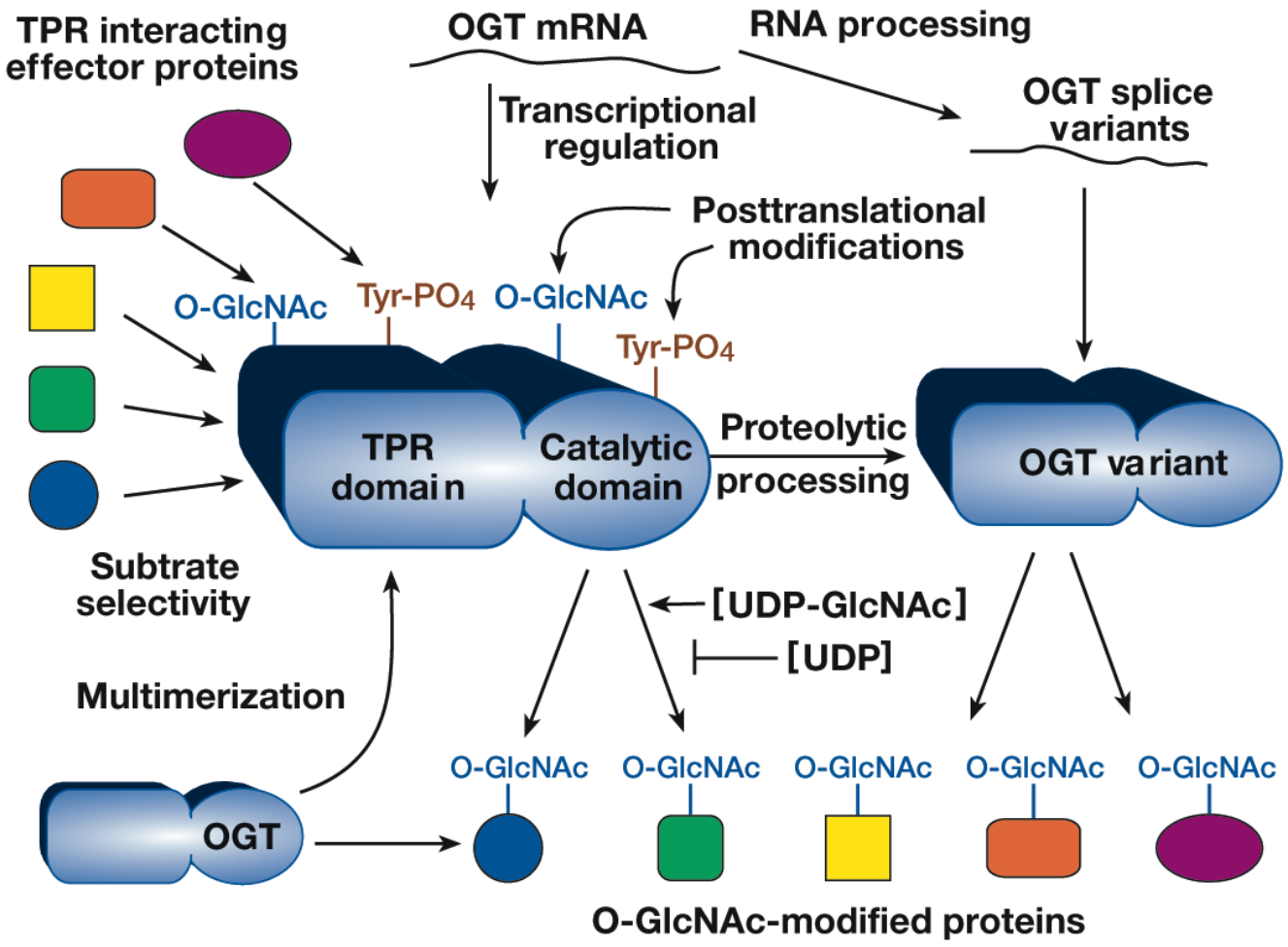
No canonical consensus sequence for O-GlcNAc addition exists in proteins

O-GlcNAc is Linked to Glucose Metabolism and UDP-GlcNAc Levels



O-GlcNAc is a reversible modification

The O-GlcNAc Transferase (OGT) is Regulated by Multiple Mechanisms



O-GlcNAc isFound on Many Hundreds of Proteins (Substrates) and Appears Involved in Numerous Cellular Processes