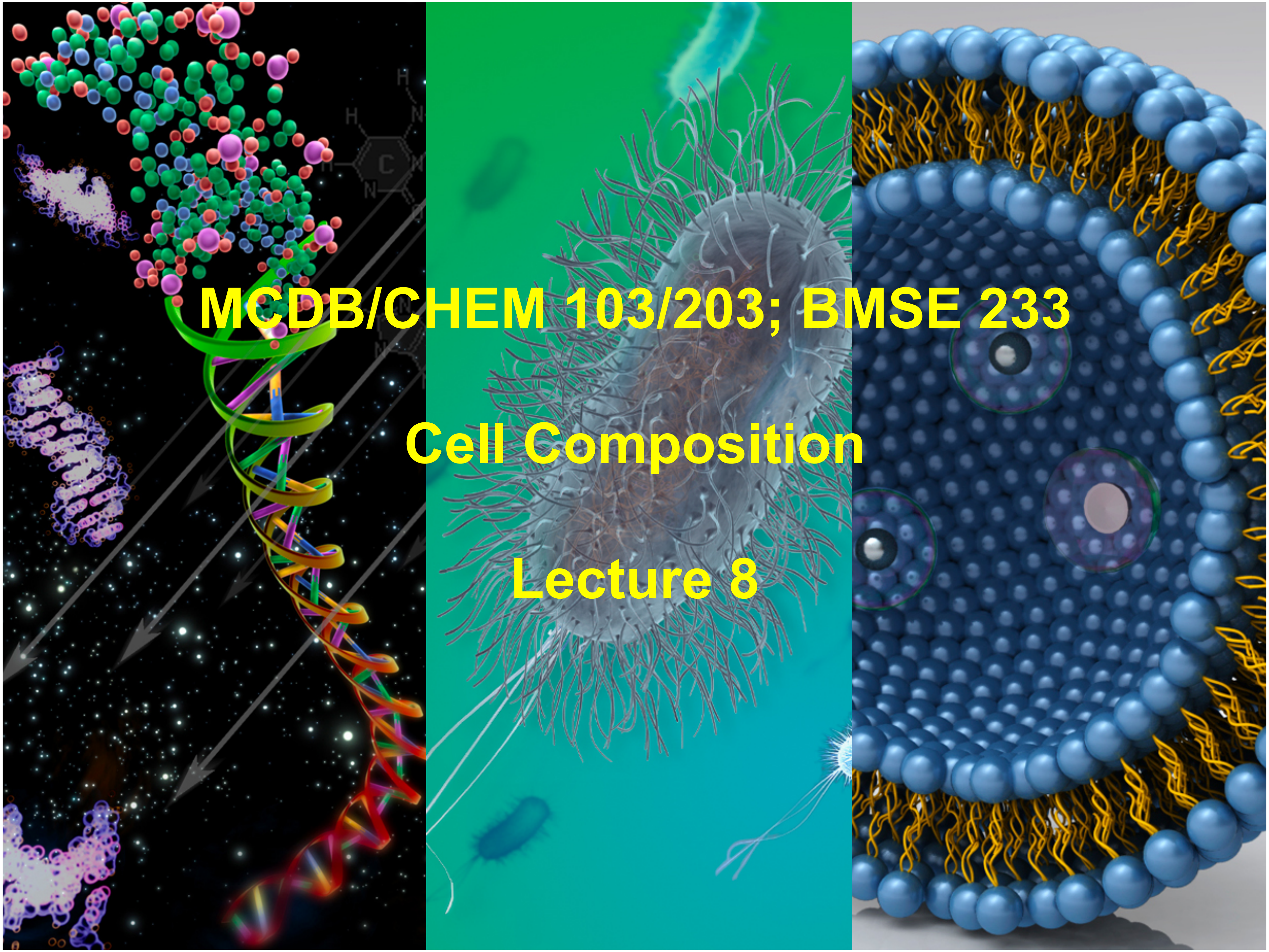
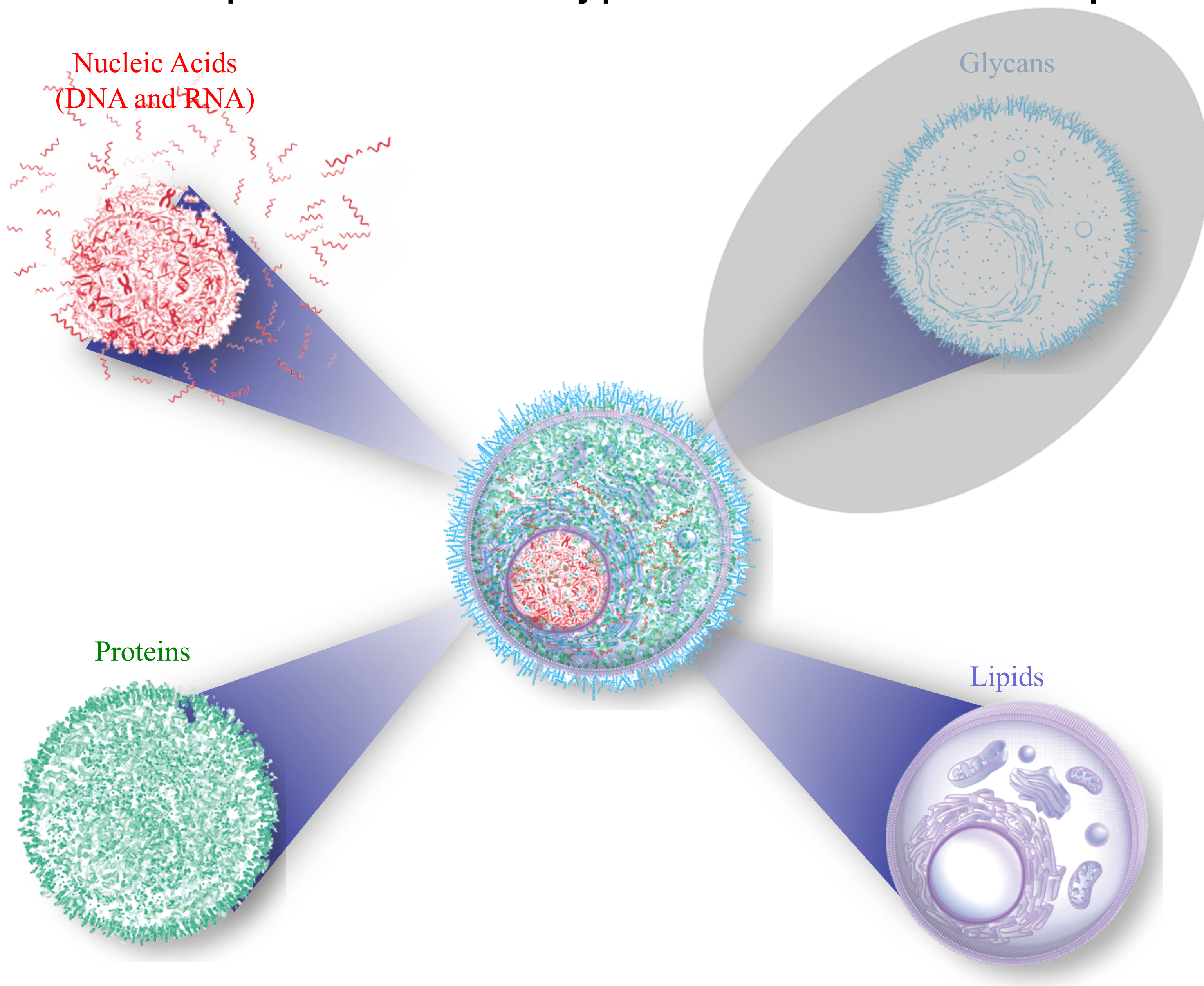


MCDB/CHEM 103/203; BMSE 233

Cell Composition

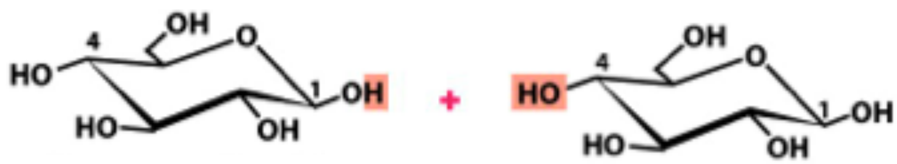
Lecture 8

Cells are Composed of Four Types of Molecular Components

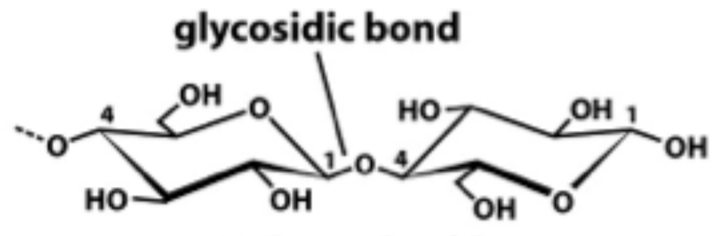


Glycans are Monosaccharides Linked to Other Molecules by the Glycosidic Bond

(Glycans are also sometimes called Polysaccharides, Carbohydrates, & Oligosaccharides)



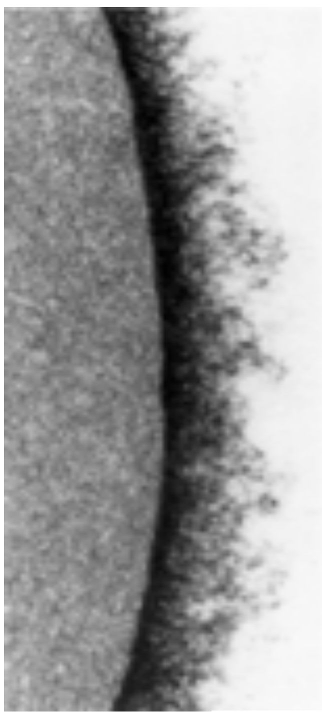
Monosaccharides

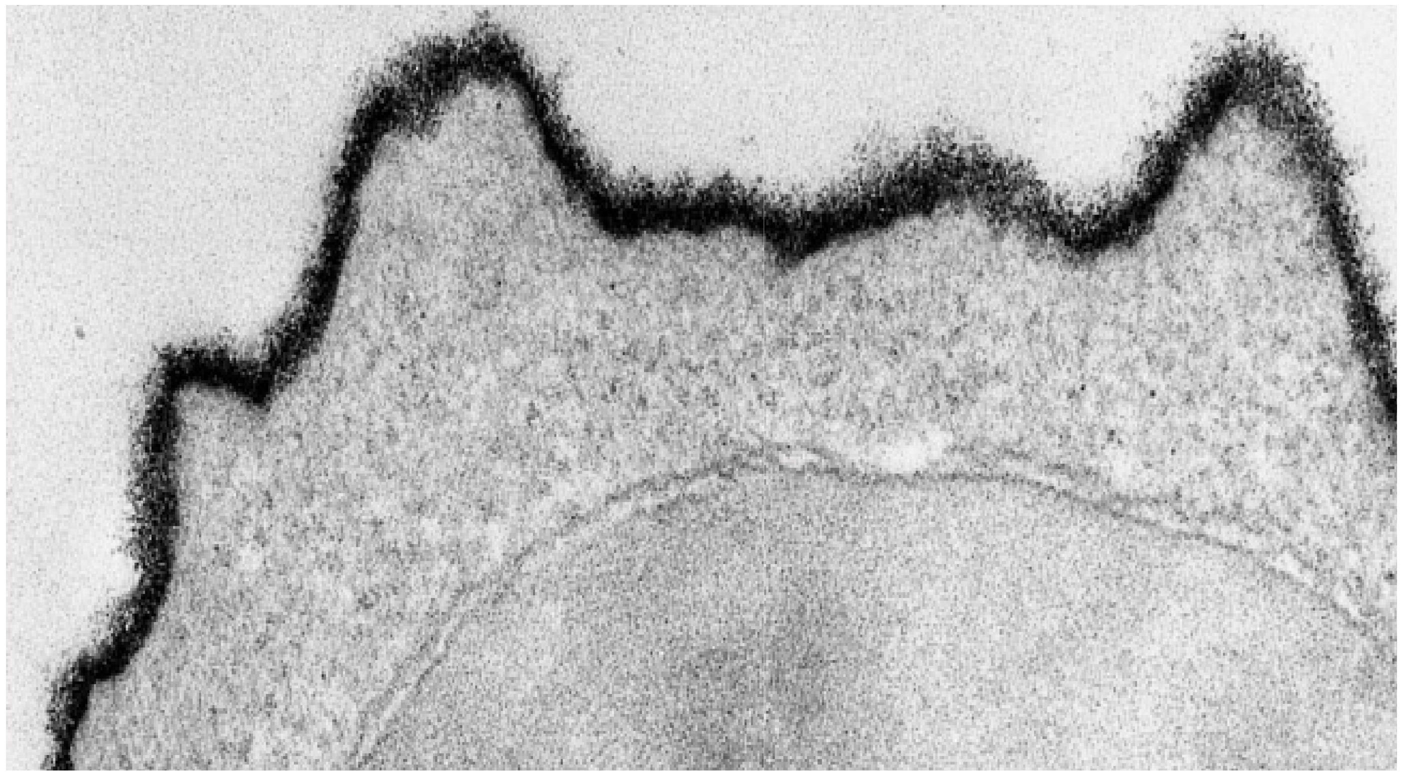


Glycan

Monosaccharides are joined together to make glycans that are often termed oligosaccharides or polysaccharides. Typically, the term oligosaccharide refers to any glycan that contains a small number (2–20) of monosaccharides connected by glycosidic bonds. The term polysaccharide is typically used to denote any linear or branched polymer consisting of monosaccharide residues. Thus, the relationship of monosaccharides to oligosaccharides or polysaccharides is analogous to that of amino acids to proteins, or nucleotides to nucleic acids.

Glycans Cover the Surfaces of All Cells in a "Glycocalyx" (~200nm thick)



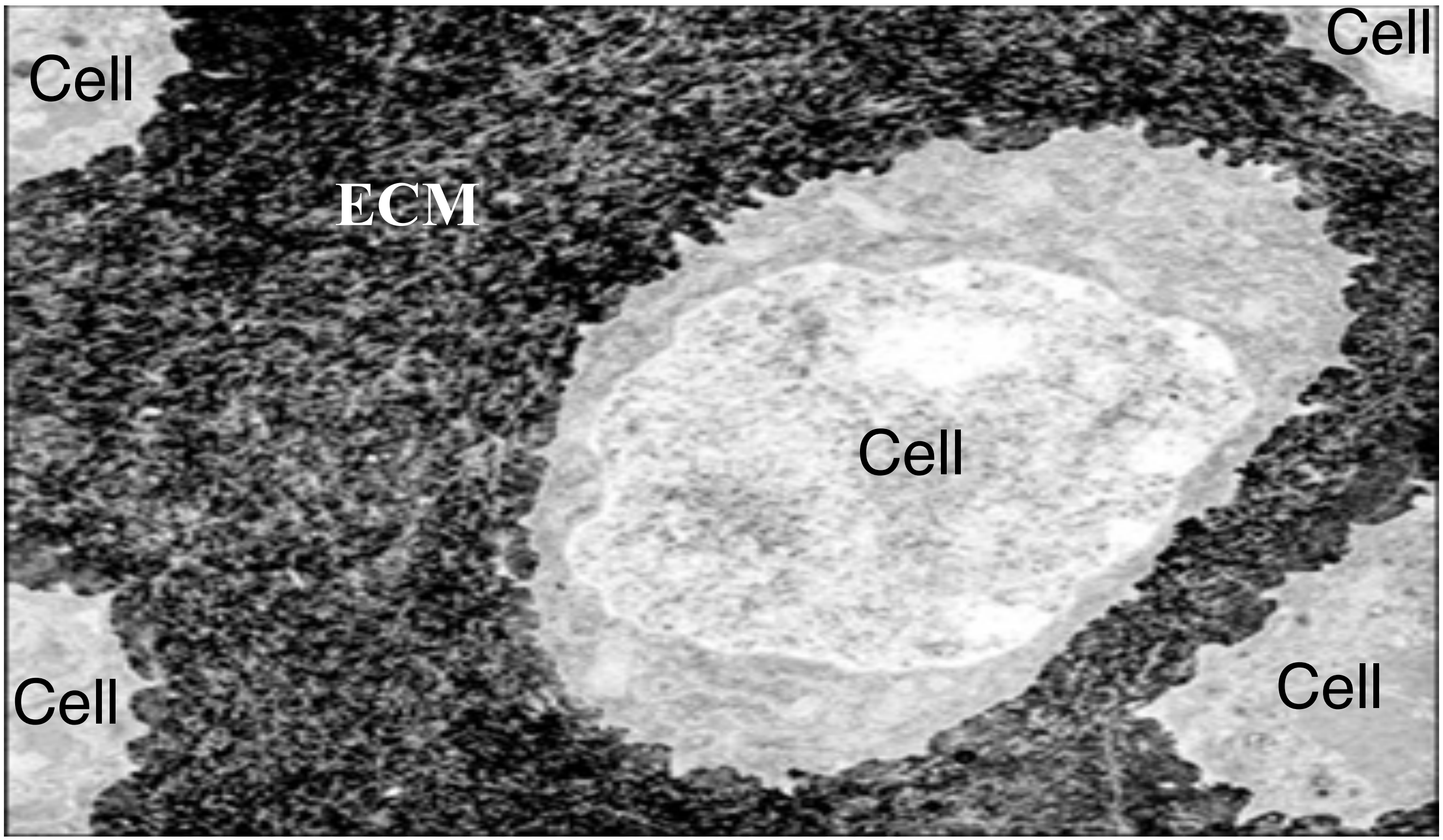


Red Blood Cell

White Blood Cell

Electron micrographs stained with Ruthenim Red

Glycans are Major Constituents of the Extracellular Matrix (ECM) between Cells



Extracellular matrix: A complex array of secreted molecules including glycoproteins, proteoglycans, other glycans including hyaluronan, and structural proteins. In plants, the extracellular matrix is also referred to as the cell wall.

Functions of Glycans

Structural:

Physical barrier; Tissue structure, porosity and integrity; Protein folding and shielding from proteases and antibodies; Determinants of microbial and viral invasion

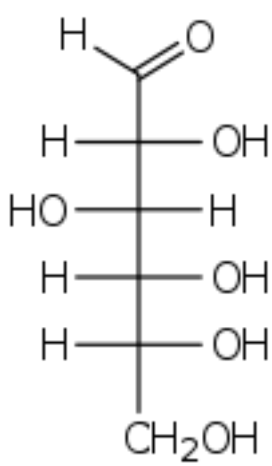
Signaling:

Energy storage (glycogen); Ligands of lectin receptors; Organization of lipid and protein complexes; Receptor activation; Storage depot for signaling molecules

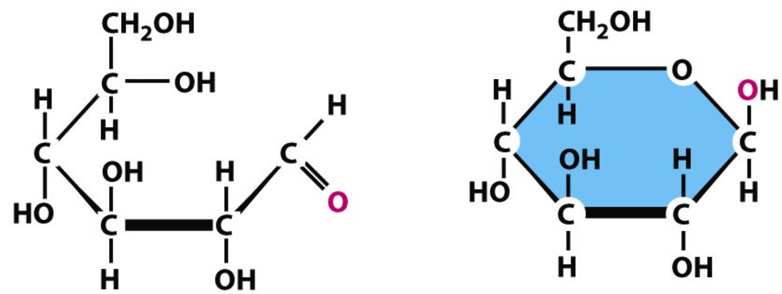
Monosaccharides are the basic building blocks of Glycans

Monosaccharides in biological systems are in equilibrium between ring and extended conformations

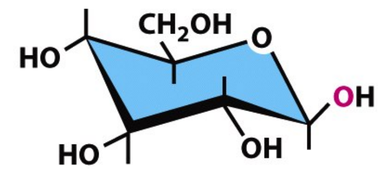
Fischer projection



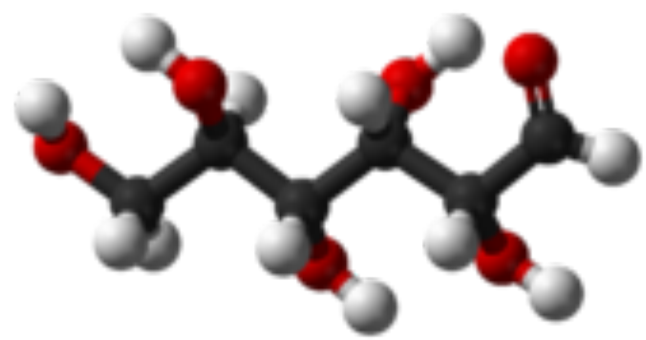
Haworth projections



Chair conformation

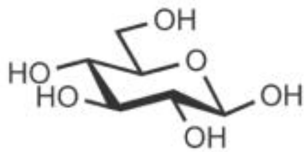


Example shown is glucose

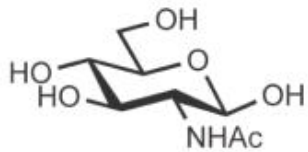


Different types of representations of glucose are shown

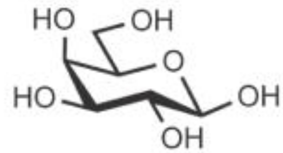
The Chair Conformation is Often Used to Represent Monosaccharides, for Example…



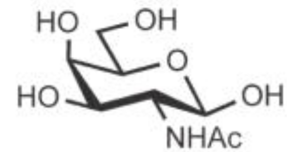
D-Glucose
(Glc)



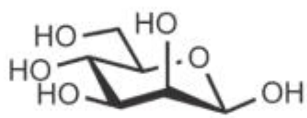
N-Acetyl-D-glucosamine
(GlcNAc)



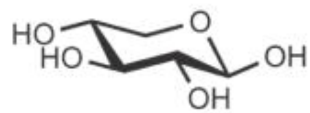
D-Galactose
(Gal)



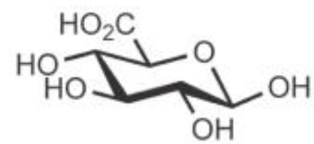
N-Acetyl-D-galactosamine
(GalNAc)



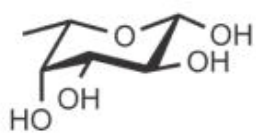
D-Mannose
(Man)



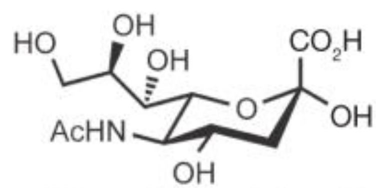
D-Xylose
(Xyl)



D-Glucuronic acid
(GlcA)



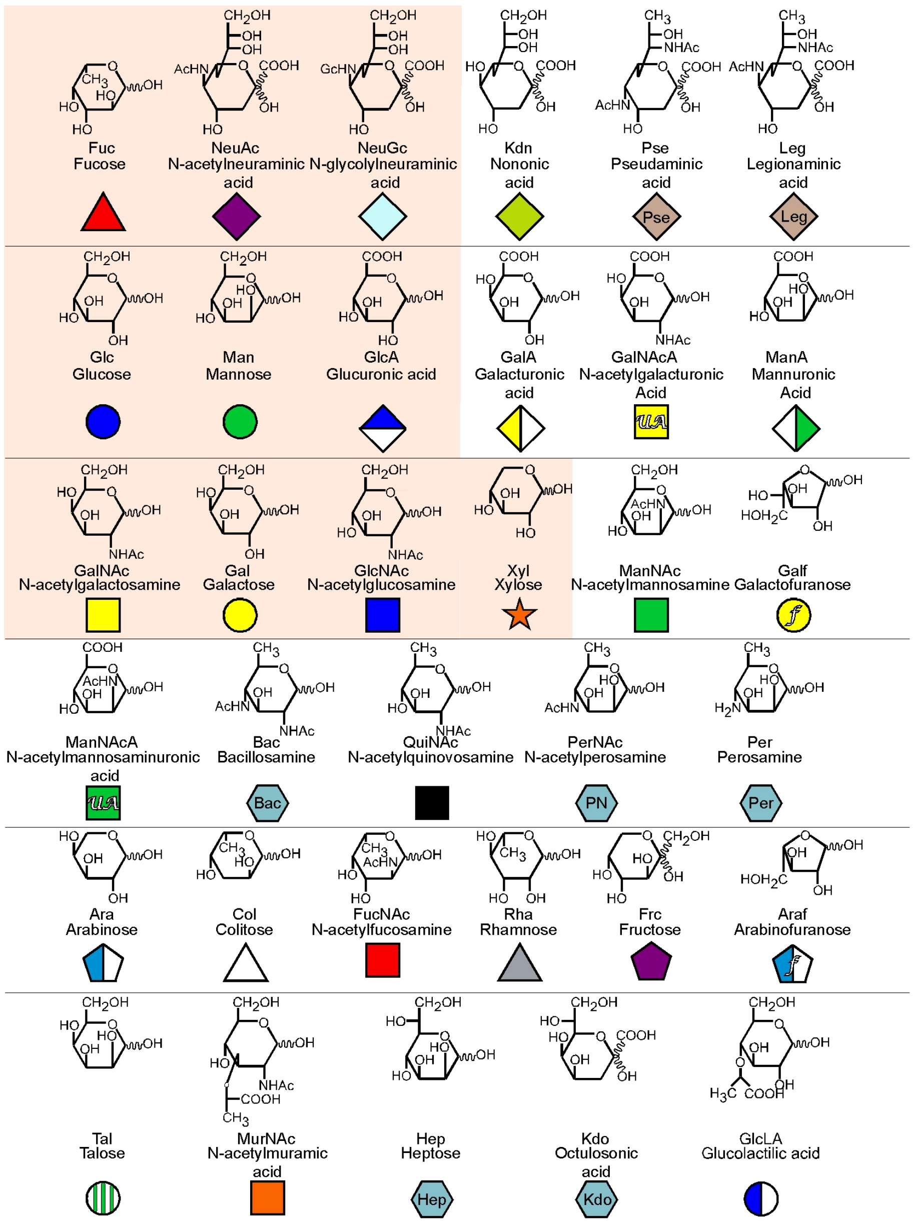
L-Fucose
(Fuc)



N-Acetylneuraminic acid
(NeuAc)

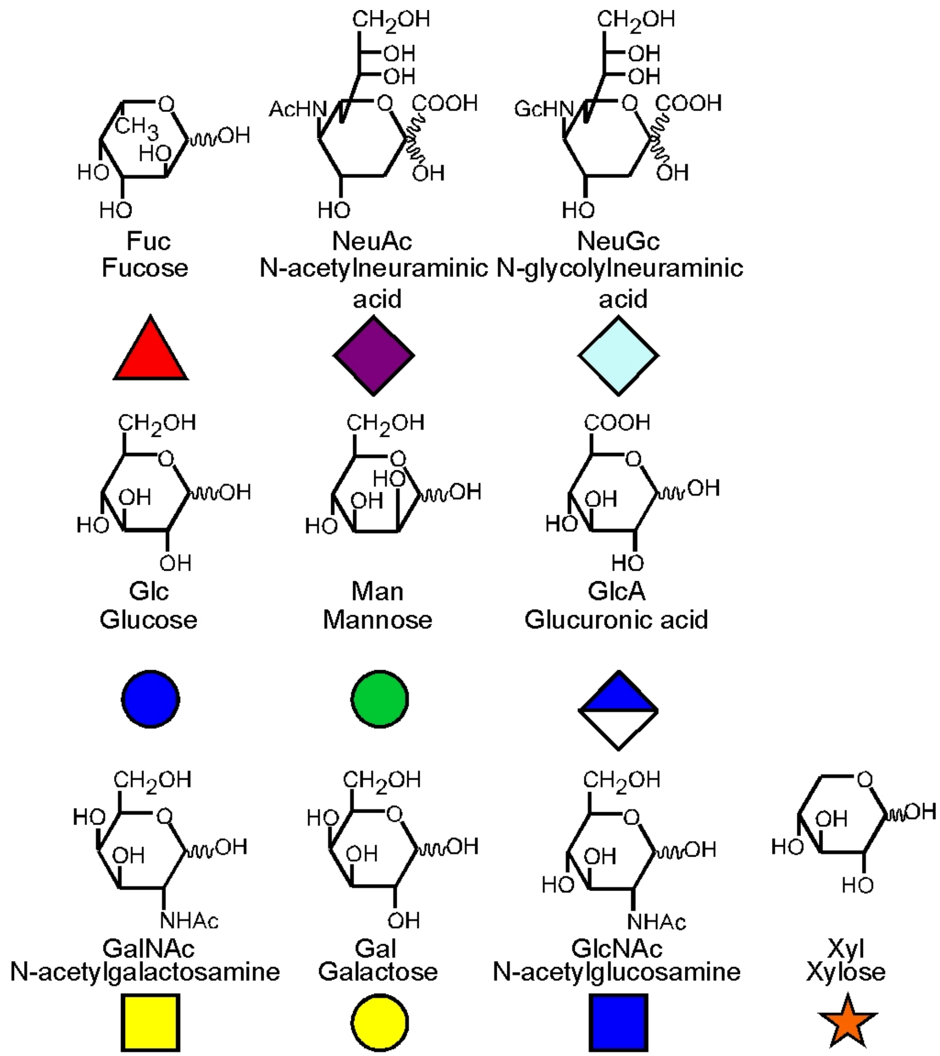
**Still difficult to visualize,
and many more exist,
a symbology is needed**

Monosaccharides Used in the Enzymatic Process Of Glycosylation Among All Life Forms

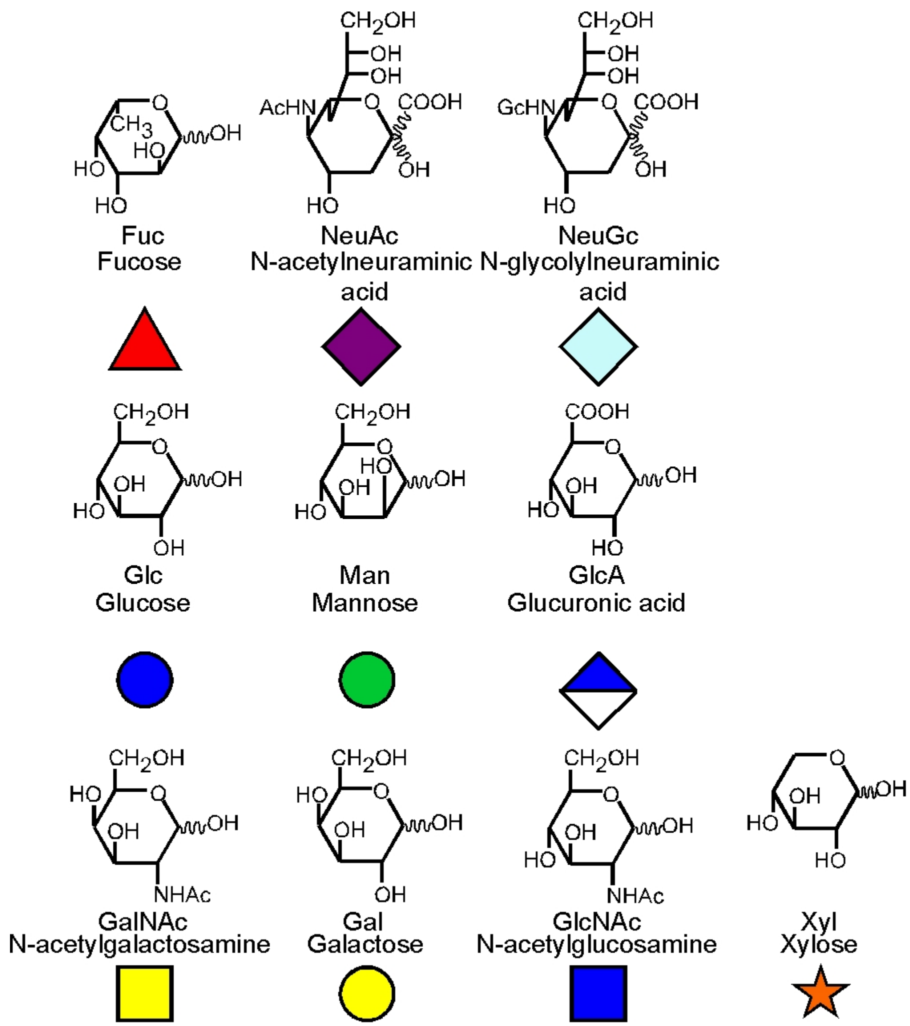


34 currently identified

Monosaccharides used in the Enzymatic Process of Glycosylation in Mammalian Cells



Monosaccharides used in Glycosylation - Mammals



Monosaccharides found in Glycans- Mammals

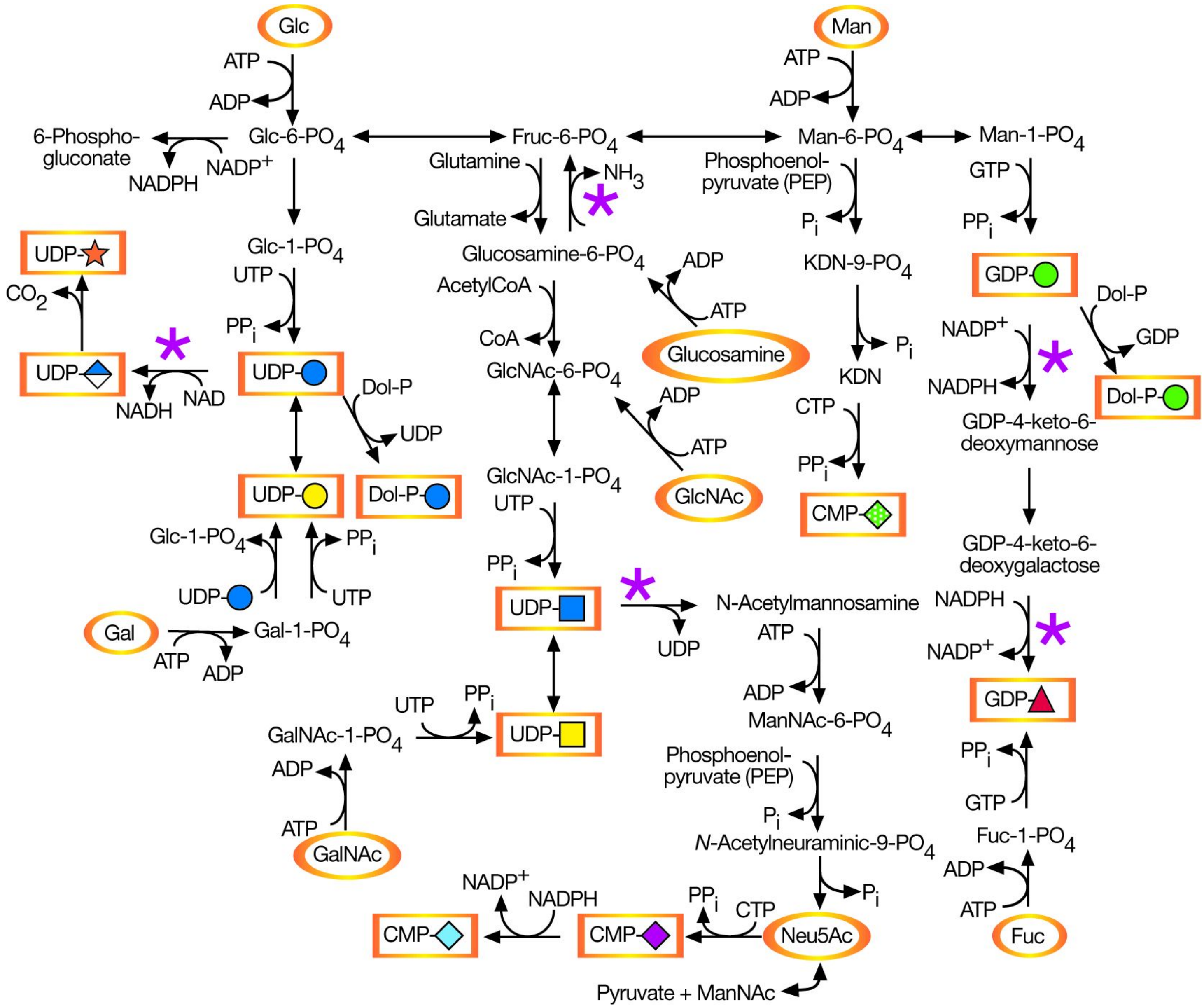
*Sialic acid is a generic term that represents both forms of neuraminic acid

There are 18 Monosaccharides Found in Glycans of Vertebrates

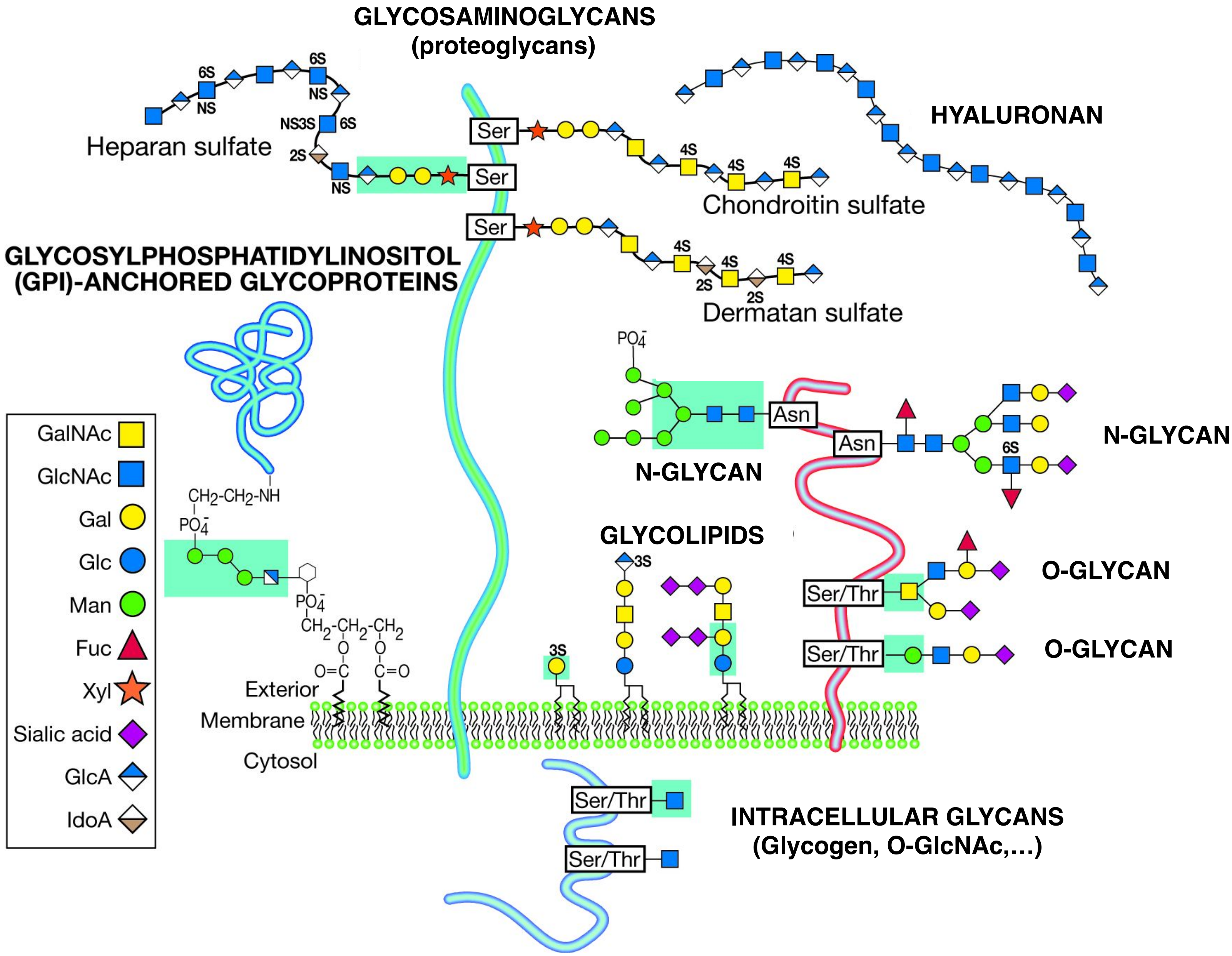
GalA, GalN, ManNAc, ManA, Kdn, and ManN are not found in Mammalian glycans.

Iduronic Acid is formed by the epimerization of Glucuronic acid in glycan chains, i.e. subsequent to Glycosylation

Biosynthesis and Interconversion of Monosaccharides: None are Essential in Human Diet for Glycan Formation

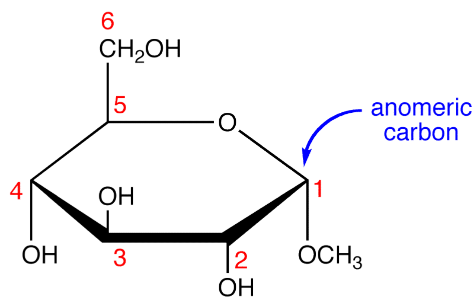


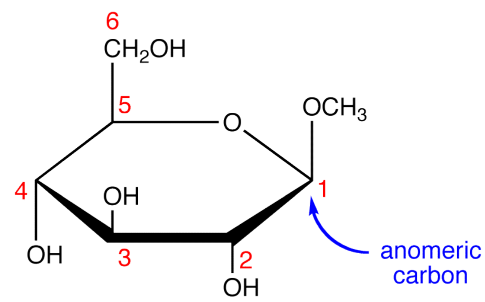
Common Classes of Vertebrate Glycans



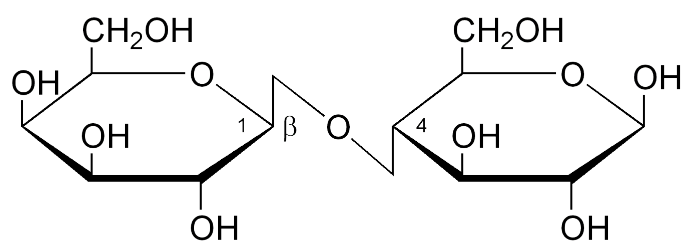
Anomeric Carbon Atoms and Positions in Monosaccharides Contribute to Glycan Structure and Function

carbons are numbered



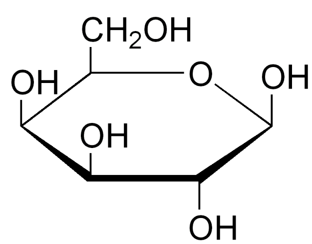


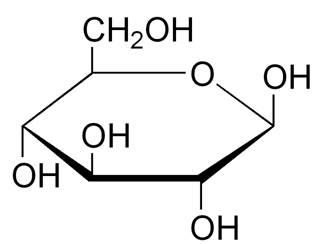
α carbon 1 anomers β



Lactose

β1−4 linkage





D-galactose D-glucose

Common Types of Glycan Projections
(note anomeric α or β linkages)

FULL REPRESENTATION

9-O-Ac-Neu5Ac*p*α2-3Gal*p*β1-4GlcNAc*p*β1-2Man*p*α1 Fuc*p*α1
6 6
Man*p*β1-4GlcNAc*p*β1-4GlcNAc*p*β1-Asn
3
3-O-SO_3Gal*p*β1-4GlcNAc*p*β1-2Man*p*α1

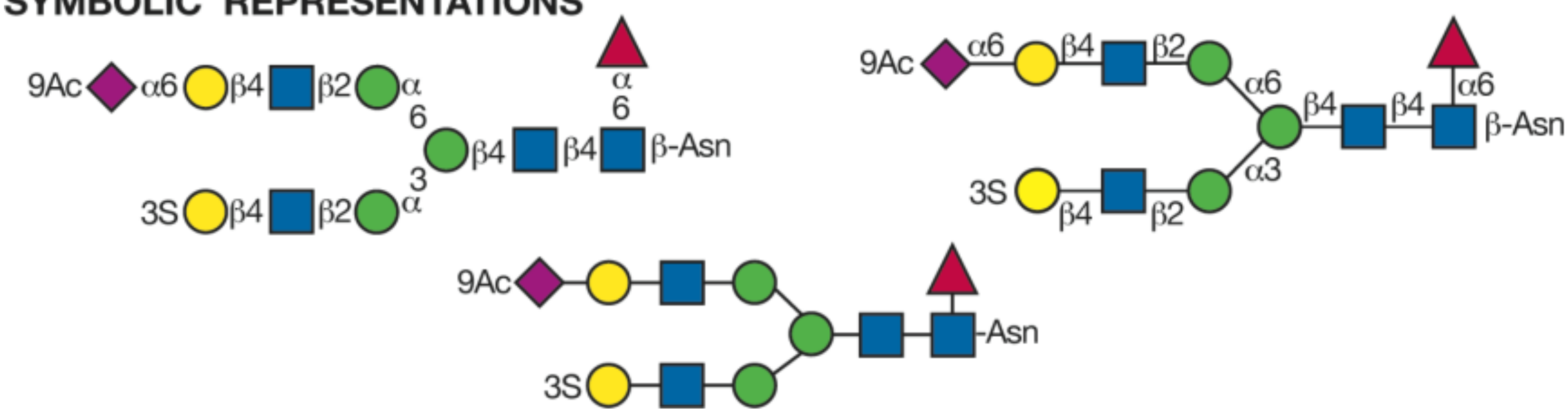
MODIFIED REPRESENTATION

9Ac-Neu5Acα2-3Galβ1-4GlcNAcβ1-2Manα1 Fucα1
6 6
Manβ1-4GlcNAcβ1-4GlcNAcβ1-Asn
3
3S-Galβ1-4GlcNAcβ1-2Manα1

SIMPLIFIED REPRESENTATION

9-O-Ac-Neu5Acα3Galβ4GlcNAcβ2Manα Fucα
6 6
Manβ4GlcNAcβ4GlcNAcβ-Asn
3
3-O-SO_3Galβ4GlcNAcβ2Manα

SYMBOLIC REPRESENTATIONS



Mammalian Glycan Linkages Produced by the Enzymatic Process of Glycosylation

DONORS	PROTEIN AND LIPID ACCEPTORS							SACCHARIDE ACCEPTORS								
	Ser/Thr (O-glycans, O-GlcNAc, glycosaminoglycans)	**Asn** (N-glycans)	**hLys** (Collagen-like domains)	**Trp** (RNase 2, IL-12, properdin)	**Tyr** (Glycogenin)	**Cer** (Glycolipids)	**PI** (GPI anchors)	Fucose △	Galactose ○	N-Acetylgalactosamine □	Glucose ●	N-Acetylglucosamine ■	Glucuronic acid ⬘	Mannose ●	Sialic acid ◆	Xylose ☆
GDP–△	α1	–	–	–	–	–	–	–	α1-2	–	–	α1-3 α1-4 α1-6	–	–	–	–
UDP–○	–	–	β1	–	–	β1	–	–	α1-3 α1-4 β1-3	β1-3	β1-4	β1-3 β1-4	–	–	–	β1-4
UDP–□	α1	–	–	–	–	–	–	–	α1-3 β1-3 β1-4	α1-3 α1-6	–	β1-4	β1-4	–	–	–
UDP–●	β1	β1	–	–	α1	β1	–	β1-3	α1-2	–	α1-2 α1-3	–	–	α1-3	–	–
UDP–■	β1	*	–	–	–	–	α1	β1-3	β1-3 β1-6	β1-6	–	α1-6 β1-4	α1-4 β1-4	β1-2	–	–
UDP–⬘	–	–	–	–	–	–	–	–	β1-3 β1-4	β1-3	–	β1-3 β1-4	–	–	–	–
GDP–●	α1	–	–	α1	–	–	–	–	–	–	–	α1-4 β1-4	–	α1-2 α1-3 α1-6	–	–
CMP–◆	–	–	–	–	–	–	–	–	α2-3 α2-6	α2-6	–	–	–	–	α2-8	–
UDP–☆	β1	–	–	–	–	–	–	–	–	–	α1-3	–	–	–	–	α1-3

Amino acid–consensus sequences or glycosylation motifs for the formation of glycopeptide bonds

Glycopeptide bond	**Consensus sequence or peptide motif**
GlcNAc-β-Asn	Asn-X-Ser/Thr (X = any amino acid except Pro)
Glc-β-Asn	Asn-X-Ser/Thr
GalNAc-α-Ser/Thr	repeat domains rich in Ser, Thr, Pro, Gly, Ala in no special sequence
GlcNAc-α-Thr	Thr-rich domain near Pro residues
GlcNAc-β-Ser/Thr	Ser/Thr-rich domains near Pro, Val, Ala, Gly
Man-α-Ser/Thr α	Ser/Thr-rich domains
Fuc-α-Ser/Thr	EGF modules (Cys-X-X-Gly-Gly-Thr/Ser-Cys) TSR modules (TrpX_5CysX_{2-3}Ser/ThrCysX_2Gly)
Glc-β-Ser	EGF modules (Cys-X-Ser-X-Pro-Cys)
Xyl-β-Ser	Ser-Gly (in the vicinity of one or more acidic

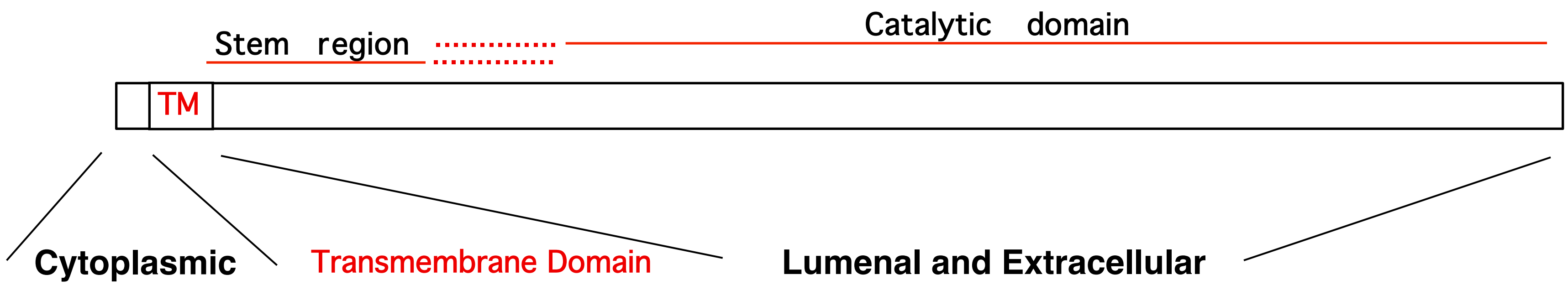
Structural Features of Glycans and Glycosidic Bonds

Linkages can include identical and different monosaccharides

Linkages are defined by carbon position

Linkage are also defined as α or β anomeric states

~250 Genes Encode the Enzymes of Mammalian Glycosylation



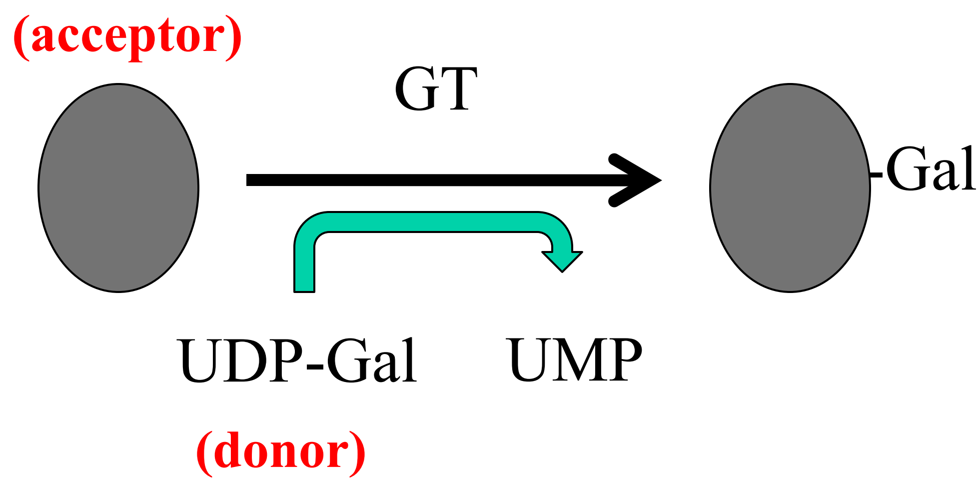
Glycosyltransferases	Glycosidases	Glycan Modifiers
N-Acetylglucosaminyltransferases	Alpha-Glucosidases	Sulfotransferases
N-Acetylgalactosaminyltransferases	Galactosidases	O-Acetyltransferases
Galactosyltransferases	Sialidases	
Sialyltransferases	Fucosidases	
Fucosyltransferases	Alpha-Mannosidases	
Mannosyltransferases		
Glucuronosyltransferases		
Xylosyltransferases		

Not including enzymes of monosaccharide donor synthesis and mechanisms of transport

Glycosyltransferases Require a High-Energy Monosaccharide Donor and a Monosaccharide or Aglycone Acceptor

Activated sugar donors

Sugar	Activated form
Glc	] UDP-sugar
Gal	
GlcNAc	
GalNAc	
GlcA	
Xyl	
Man	] GDP-sugar
Fuc	
Sia	] CMP-Sia



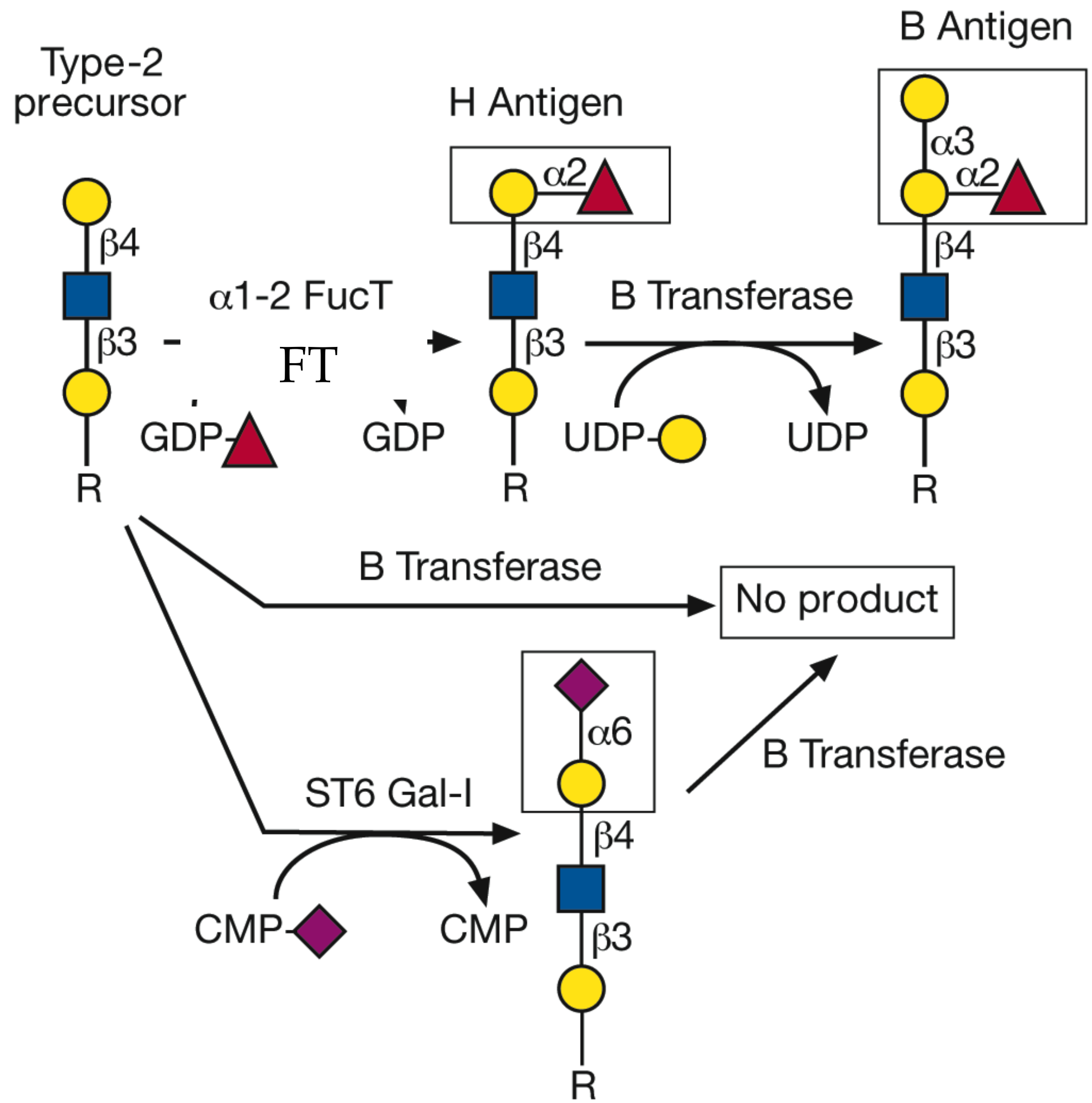
UDP: Uridine Di-Phosphate

GDP: Guanine Di-Phosphate

CMP: Cytidine Mono-Phosphate

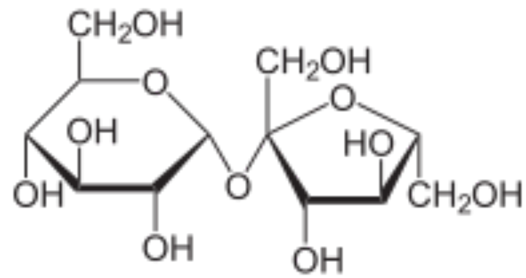
Aglycone: an monosaccharide accepter that is not a monosaccharide; ex. amino acid

Strict Acceptor Substrate Specificity of Glycosyltransferases



Stepwise process of glycan synthesis: product becomes substrate for next enzyme

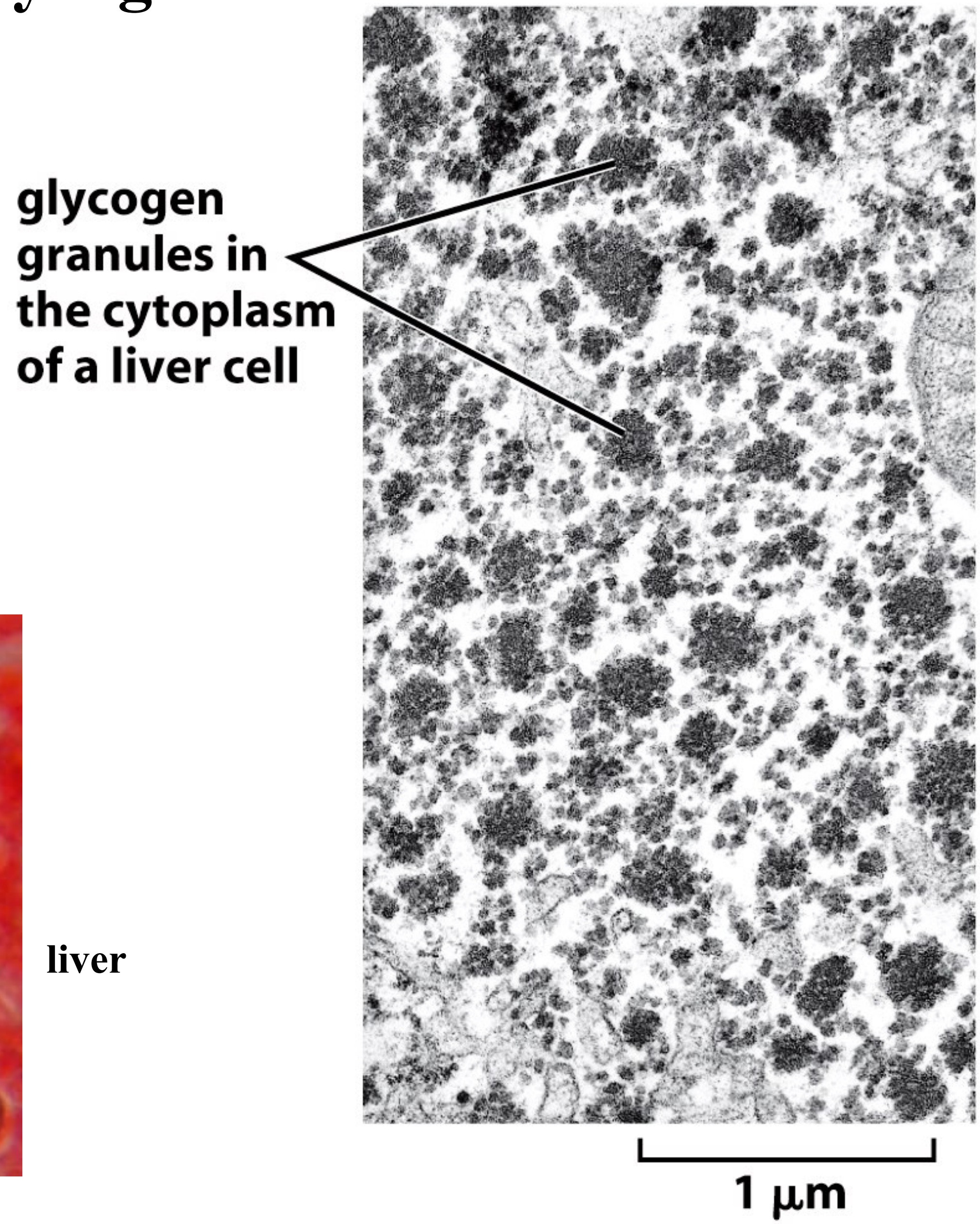
Sucrose (Table Sugar) is a Glycan made in Nature only by Plants and Cyanobacteria



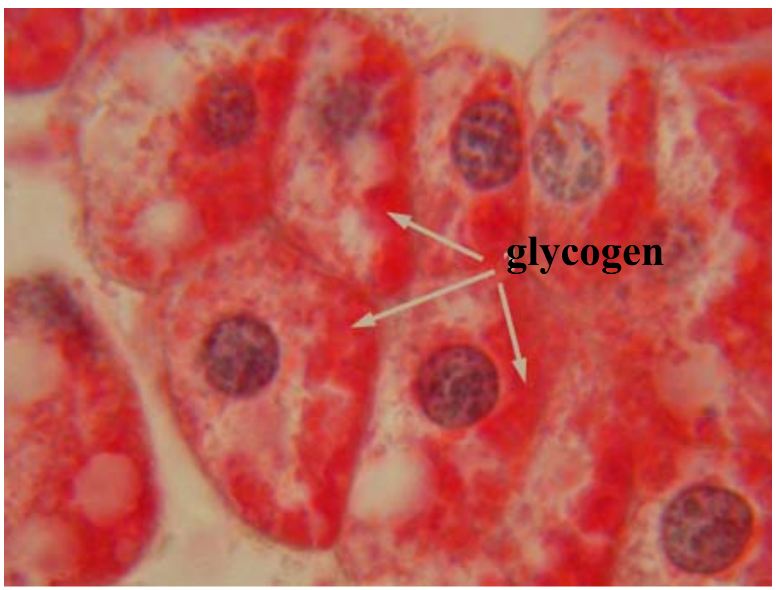
Sucrose is a di-saccharide of glucose and fructose

broken down to constituent monosaccharides in the human gut

Glucose is Stored as Glycogen in Animals

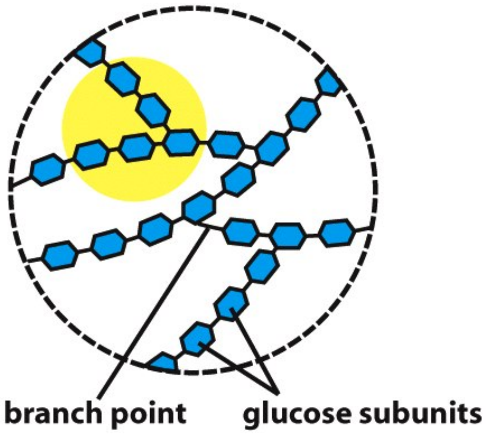


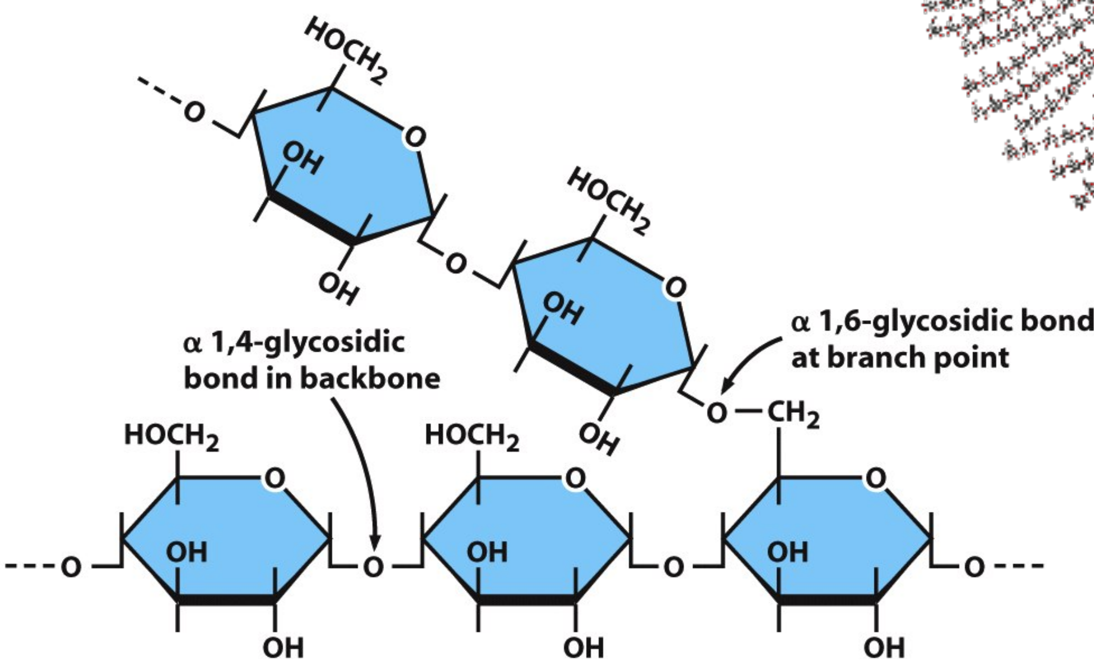
Glycogen is made primarily by the liver and muscles, but can also be made within the brain and stomach.

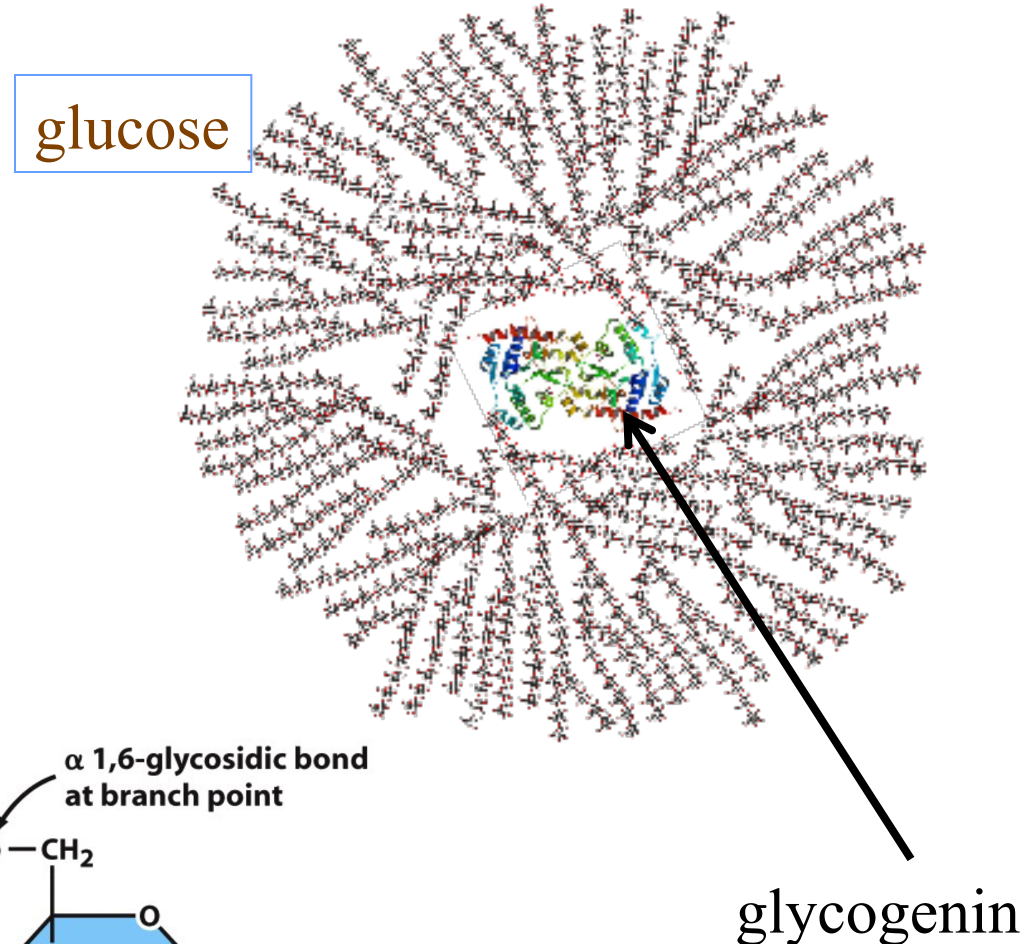


liver

Glycogen is a Large Number of Glucose Molecules Linked to Themselves and a Core Protein



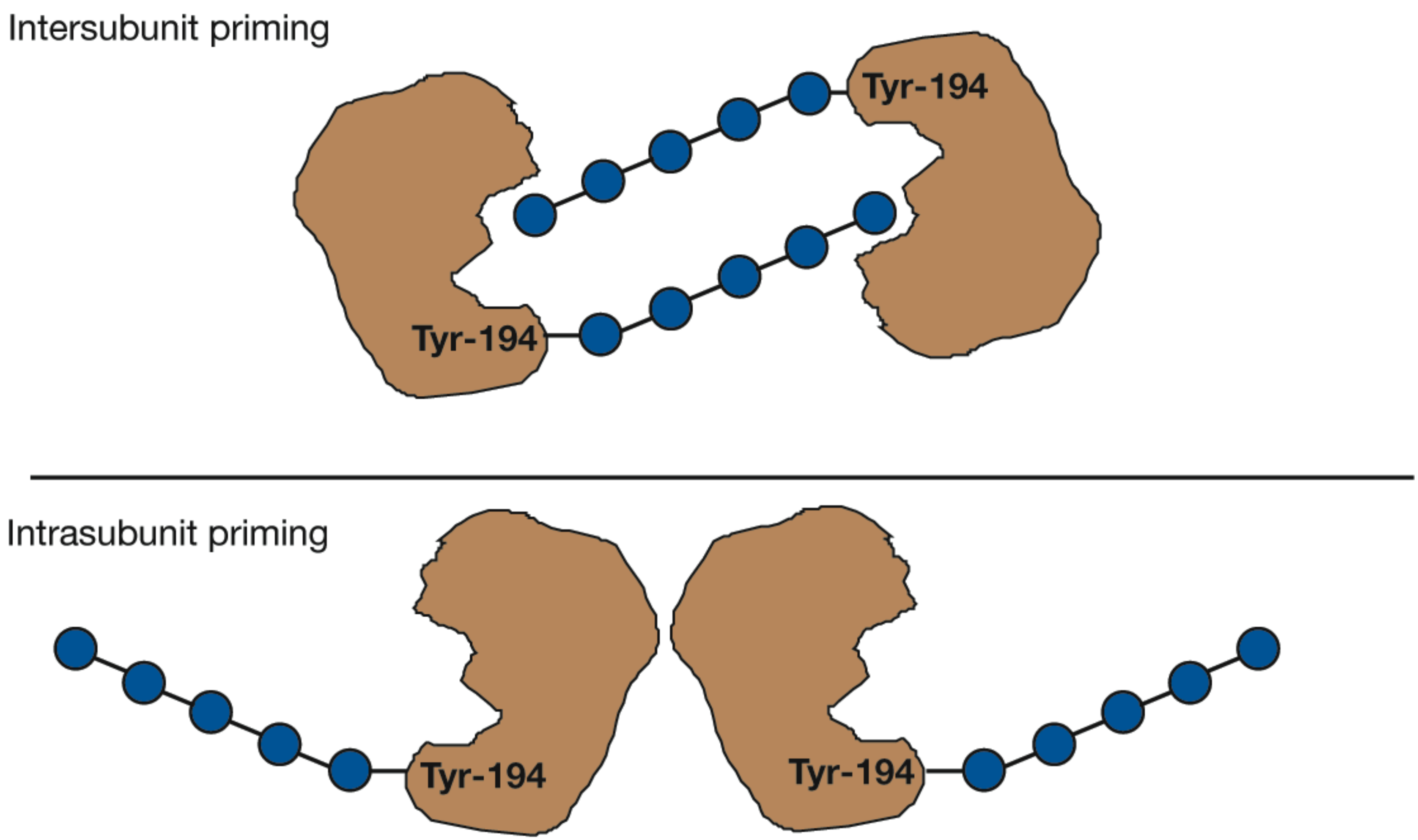




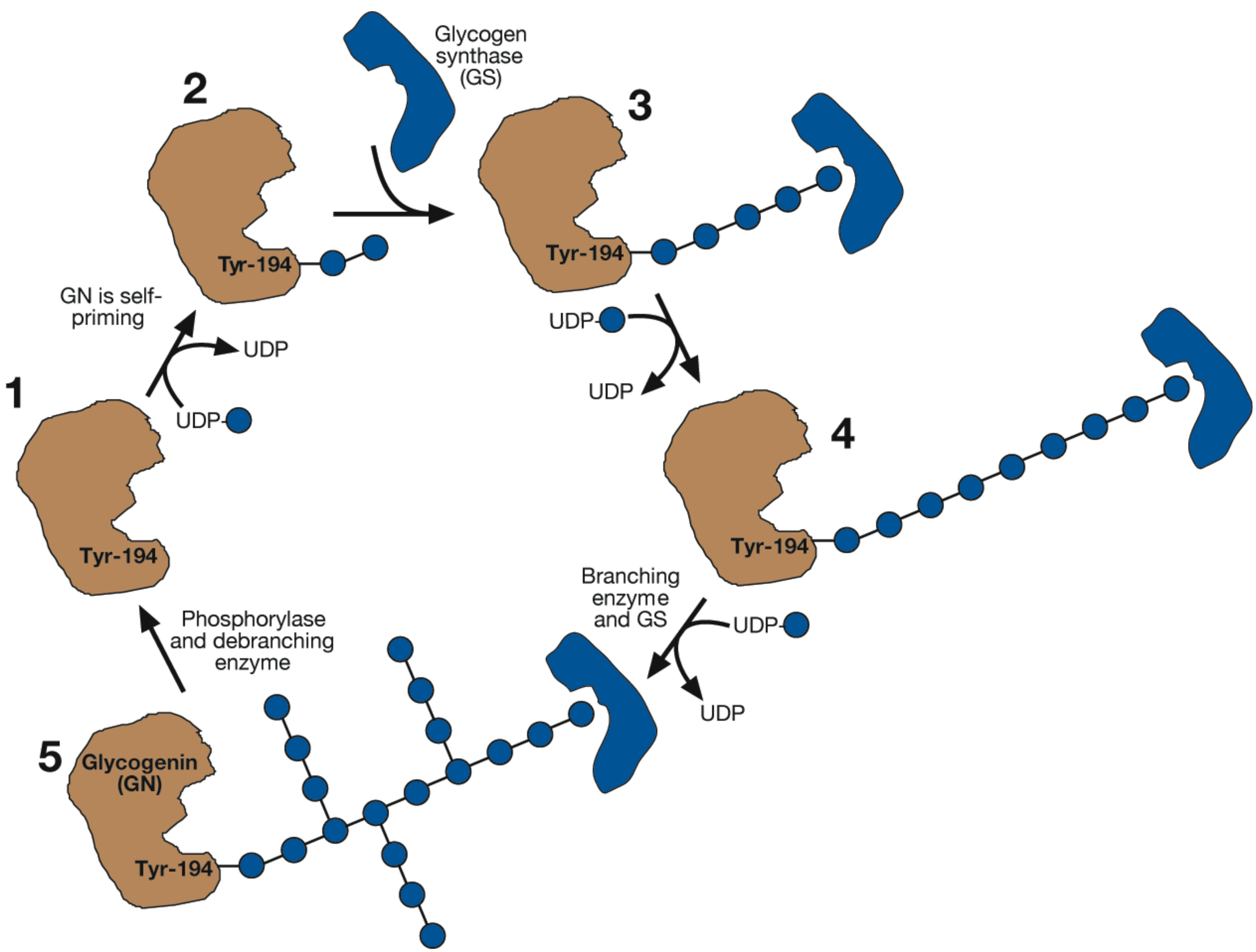
Glycogenin was the first glycoprotein discovered

Opposing Models for the Self-Glucosylation of Glycogenin

**Glycogenin is a glycoprotein and enzyme involved in converting glucose to glycogen.
It acts as a primer, by adding the first few glucose molecules,
after which other enzymes take over.**

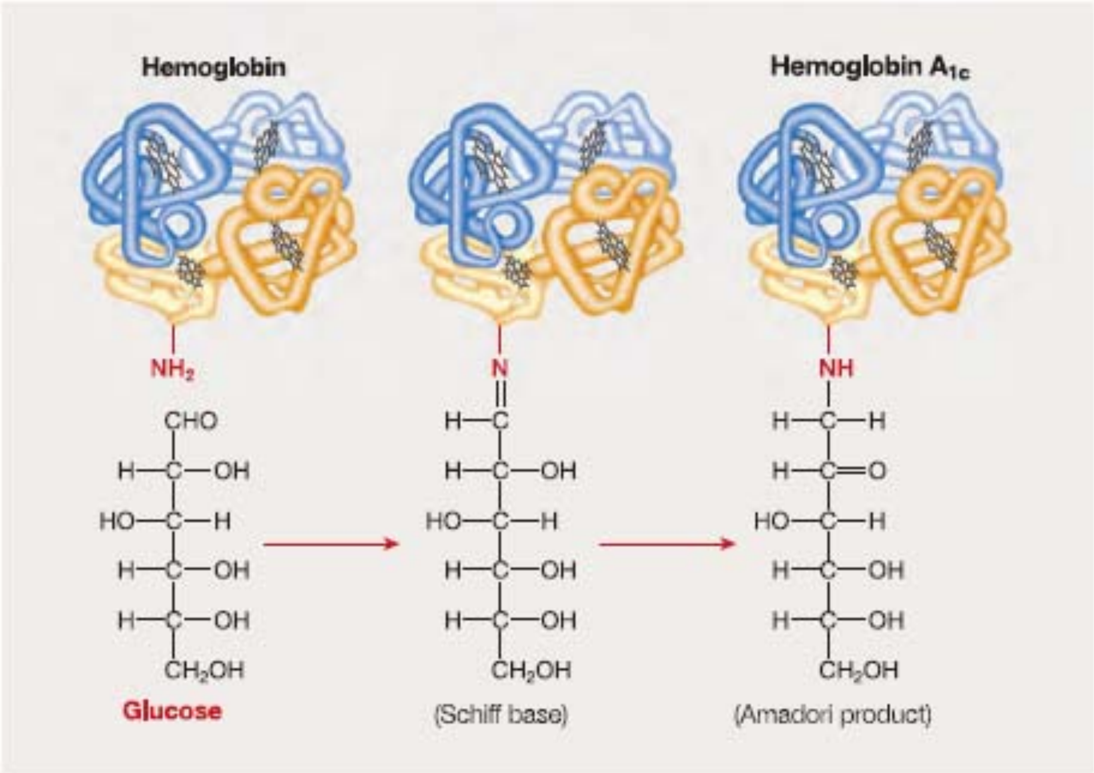


Model for Glycogen Biosynthesis via Glycogenin (GN), Glycogen Synthase (GS), and a Branching Enzyme



What is Glycation?

Glycation is the non-enzymatic covalent bonding of a sugar molecule (such as glucose or fructose) to substances including proteins.

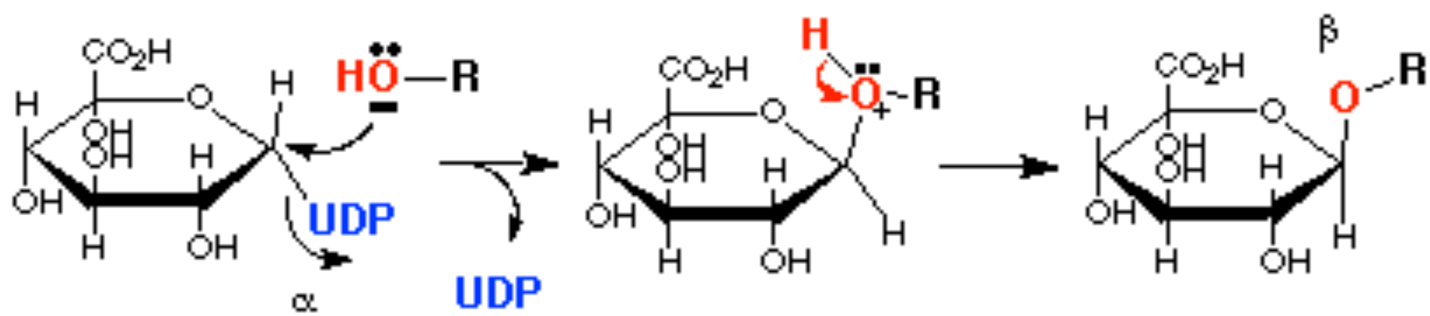


Glucose is the primary metabolic fuel for humans. It is more stable than galactose and is less susceptible to the non-enzymatic cross-linking of glucose to proteins and the formation of advanced glycation end products (AGEs).

What is Glucuronidation?

Glucuronidation is the enzymatic addition of glucuronic acid to a substrate. Glucuronidation is often involved in xenobiotic metabolism of substances by the liver such as drugs, pollutants, bilirubin, androgens, estrogens, mineralocorticoids, glucocorticoids, fatty acid derivatives, retinoids, and bile acids. These linkages involve glycosidic bonds.

Glucuronidation occurs mainly in the liver, although the enzymes responsible for its catalysis, the UDP-glucuronyltransferases, have been found in all major body organs.



UDP-glucuronic acid reacts with alcohol (-OH), carboxylic acids (CO_2OH), amines and amides (NH_2), and thiols (SH).

Lectins Can Decode the Information in Glycans

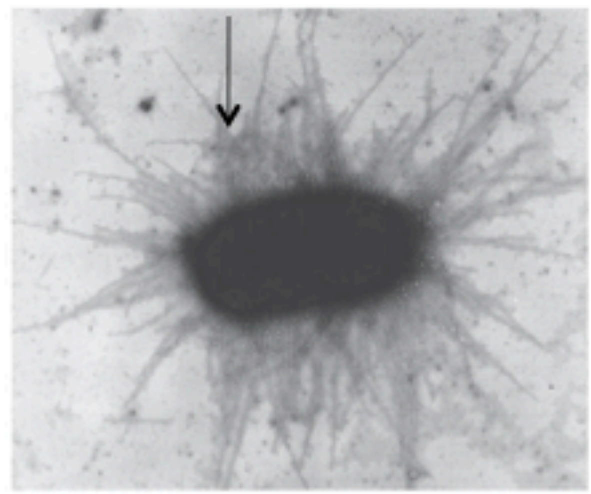
Lectins are sugar-binding proteins (not to be confused with glycoproteins, which are proteins containing sugar chains or residues) that are highly specific for their sugar moieties. They play a role in biological recognition and signaling.

Plant lectins first identified in 1888 as agglutininins.

Viral and bacterial lectins identified ~1950s

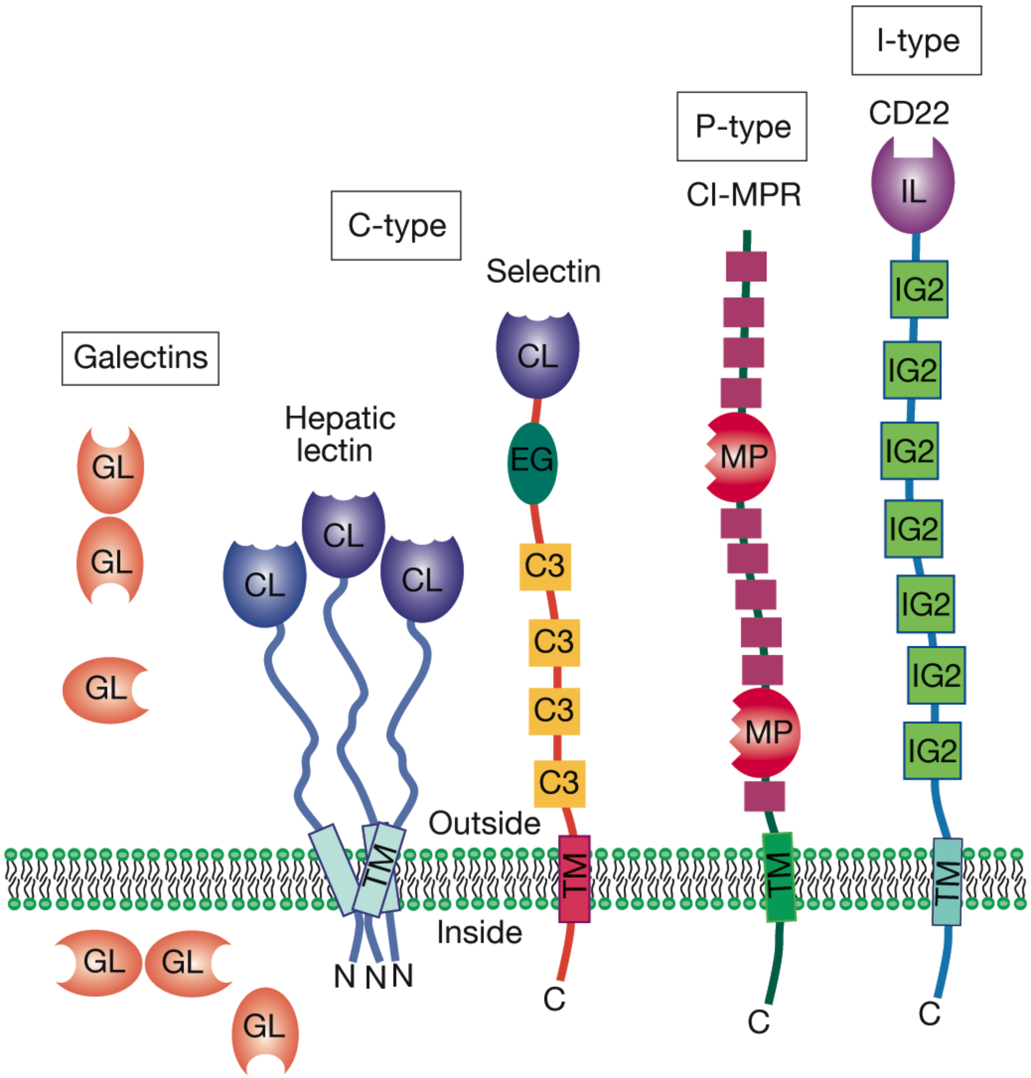
Mammalian lectins identified 1960s

Bacterial fimbriae or pili



Bacterial lectins reside in the fimbriae or pili

Schematic Examples of Major Types of Animal Lectins (exist as cytosolic, secreted, and membrane proteins)



Examples of some of the major families are shown. The emphasis is on the extracellular domain structure and topology. The following are the defined glycan-binding domains (GRDs) shown: (CL) C-type lectin GRD; (GL) S-type lectin GRD; (MP) P-type lectin GRD; (IL) I-type lectin GRD. Other domains are (EG) EGF-like domain; (IG2) immunoglobulin C2-set domain; (TM) transmembrane region; and (C3) complement regulatory repeat. The number of domains underlying the GRD can vary among family members.

Over 150 lectins identified, many more likely exist

Glycans and Lectins in Protein Binding and Function