Introduction to Glycobiology

<u>Date</u>	<u>Subject</u>	Discussion leader
Apr 20	The Glycobiology Landscape: Sugars as Language	Ron Schnaar
Apr 21	Structures & Functions of Glycoproteins	Natasha Zachara
Apr 22	Structures & Functions of Hyaluronan & Proteoglycans	Ron Midura
Apr 23	Structures & Functions of Glycolipids	Ron Schnaar
Apr 24	Protein-Glycan Recognition	Ron Schnaar
Apr 27	Glycan Binding Protein Functions	Natasha Zachara

Faculty

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<u>GoToMeeting link (primary)</u>: https://www.gotomeet.me/RonaldSchnaar

Zoom EMERGENCY link (backup):

https://jhjhm.zoom.us/j/96923102132?pwd=SURoZUpXUHpaOUhFSkhvUzcONEJhQT09 Password: Neu5Ac

DropBox course materials:

https://www.dropbox.com/sh/c4urzf3m2z0p2vk/AABqEZ1E0D25IbUBX-0yc5LDa?dl=0 Password: Neu5Ac



OXFORD

"Concise, clear introduction"



Maureen E. Taylor and Kurt Drickamer



Oxford University Press, 2011

"Thorough, detailed, comprehensive"



Cold Spring Harbor Laboratory Press, 2017 Content freely available: <u>http://www.ncbi.nlm.nih.gov/books/NBK310274</u>

*Disclaimer: Dr. Schnaar is a co-editor.

** He put a lot of effort into this and won't make a friggin' cent

NCBI Glycans https://www.ncbi.nlm.nih.gov/glycans/

Definitions

- Glycobiology The study of glycan <u>functions</u> related to their structures, recognition, biosynthesis, and molecular context (biological scaffolds, e.g. glycolipids & glycoproteins).
- Glycoscience Glycobiology & <u>chemistry</u> including chemical synthesis, chemoenzymatic synthesis, metabolic engineering, glycomimetics, 3D structures. Includes glycans in material sciences and plant and bacterial polysaccharides
- Glycomics <u>Analytical</u> glycoscience & glycan <u>bioinformatics</u>. The "glycome" is the total complement of glycans in a cell or organism



"The fear of getting involved in understanding any biological processes in which glycans play a major role" (Ajit Varki)

Where does this fear come from?





Monosaccharide Query Results

	Results 1 - 10 of 776 (Page 1 of 78) • prev • next		• prev • next
d	Name (N	Name (MsDB) Name (Car	
	b-dglc-H	EX-1:5 (2d:1)n-acetyl	b-D-GlcpNAc
	b-dgal-H	EX-1:5	b-D-Galp

 3
 a-dman-HEX

 4
 b-dglc-HEX-1

 5
 b-dman-HEX

 6
 a-dgro-dgal-N

 7
 a-lgal-HEX-1:

 8
 a-dglc-HEX-1:

 9
 a-lman-HEX-1:

 10
 a-dgal-HEX-1:

Invited Commentary *Glycobiology* 4:759-767 (1994)

A calculation of all possible oligosaccharide isomers both branched and linear yields 1.05×10^{12} structures for a reducing hexasaccharide: the *Isomer Barrier* to development of single-method saccharide sequencing or synthesis systems

Roger A.Laine

Departments of Biochemis The Louisiana Agricultura



Special Invited Review Glycobiology 27:3-49 (2017)

Biological roles of glycans

Ajit Varki

Departments of Medicine and Cellular & Molecular Medicine, Glycobiology Research and Training Center, University of California at San Diego, La Jolla, CA 92093-0687, USA

"....any attempt at being comprehensive is now impractical, and the knowledge base of a single individual cannot do justice to this vast and complex field."





Schnaar, J Leuk Biol 99:825, 2016

The Glycobiology Landscape: Sugars as language

Glycans: the "missing mass" of the biological universe
 Monosaccharides: The alphabet of glycoscience
 The glycosidic bond and glycan nomenclature
 Major carbohydrate classes: sugars, polysaccharides, oligosaccharides and glycans
 Major glycans of mammals

Rosetta Stone, British Museum

The mammalian cell surface

The "glycocalyx" revealed (glycans stained with ruthinium red)



Majnaez-pokemb, & Senaid Sahcell Res Birg, 1925-1937, 6396 92013

"Every eukaryotic cell is covered with a dense and complex array of glycans." ... in fact...

"Evolution has failed to generate a living cell devoid of surface glycosylation" - A. Varki

The invisible fungal glycocalyx



Light (phase) micrograph of *Cryptococcus neoformans* capsule delineated by India ink. The inner circle represents the fungal cell, with the wide outer circle being the capsule.

Steenbergen et al. (2003) *Microbes and Infection* 5:667

Scanning electron micrograph of *C. neoformans* yeast cells. Van Duin et al. (2004) *Antimicrobial Agents and Chemotherapy* 48:2014



The bacterial glycocalyx



Electron microscopic thin section of *Escherichia coli* K1 Amako et al. (1988) *J Bacteriol* 170:4960

Electron microscopic thin section of *Klebsiella pneumoniae*

Amako et al. (1988) *J Bacteriol* 170:4960





The cell surface is a forest canopy of glycans

based on Ajit Varki, "Perspectives on the Future of Glycobiology," Athens, GA, 14-Mar-2011



Textbook image

Real image



The Glycobiology Landscape: Sugars as language

Glycans: the "missing mass" of the biological universe

Monosaccharides: The alphabet of glycoscience

Mammalian Glycobiology

- 9 monosaccharides
- Glucose (Glc)
- Galactose (Gal)
- Mannose (Man)
- N-Acetylglucosamine (GlcNAc)
- N-Acetylgalactosamine (GalNAc)
- **L**-Fucose (Fuc)
- Sialic Acid (Sia, Neu5Ac)
- 🛧 Xylose (Xyl)
- Glucuronic Acid (GlcA)



Seven sugars closely related to glucose



Taylor & Drickamer (2011) Introduction to Glycobiology, 3rd edition

Two important terminal sugars



Taylor & Drickamer (2011) Introduction to Glycobiology, 3rd edition

Sugars as language: Strategic placement of molecular recognition determinants



Sugars as language: Strategic placement of molecular recognition determinants

Glucose

Galactose

Mannose



Sugars as language: Strategic placement of molecular recognition determinants

Sialic Acid (Neu5Ac)





The anomeric carbon - a or β

- Glycobiologists seldom think of sugars as linear molecules
- Pentoses and hexoses are <u>predominantly</u> in their ring forms at equilibrium
- Only <u>free</u> sugars equilibrate between open chain and ring forms; when sugars are linked to one another (or an aglycone) their ring form and anomeric configuration are fixed
- There are two possible configurations at the anomeric carbon, α and β



The Glycobiology Landscape: Sugars as language

- Glycans: the "missing mass" of the biological universe
- Monosaccharides: The alphabet of glycoscience
- The glycosidic bond and glycan nomenclature

Rosetta Stone, British Museum

Sugars and linked via glycosidic bonds



When a glycosidic bond is formed the anomeric configuration is "locked"

Glycan nomenclature



Taylor & Drickamer (2011) Introduction to Glycobiology, 3rd edition

Nomenclature:

-Name the non-reducing (left-most) sugar (Gal)
-Name the anomeric configuration (β)
-Name the anomeric carbon number (1)
-Name the substituted carbon number (4)
-Name the substituted sugar (Glc)

RESULT: Gal β1-4 Glc



Branched glycan nomenclature



Neu5Ac α 2-3 Gal β 1-4 (Fuc α 1-3) GlcNAc



Symbol nomenclature for glycans



The Glycobiology Landscape: Sugars as language

- Glycans: the "missing mass" of the biological universe
- Monosaccharides: The alphabet of glycoscience
- The glycosidic bond and glycan nomenclature
- Major carbohydrate classes: sugars, polysaccharides, oligosaccharides and glycans

Sugars, polysaccharides, oligosaccharides and glycans

- Sugars: often from plants or plant polysaccharides
 [glucose, sucrose (glucose a1-2 fructose), maltose (Glc a1-4 Glc), lactose (Gal β1-4 Glc)]
- Polysaccharides: linear or branched polymers of a single sugar [cellulose, amylose (starch), glycogen, chitin]
- Oligosaccharides: groups of monosaccharides (typically 3 or more) in linear or branched glycosidic linkage [Seldom found as free structures - most often components of glycans]
- Glycans: Oligosaccharides on proteins or lipids [glycoproteins, glycolipids, proteoglycans]

Polysaccharide: cellulose



Most abundant organic compound on Earth. ~90% of cotton fiber, 50% of wood, 33% of all plant matter.



Intra- and inter-strand hydrogen bonding provides strength



http://en.wikipedia.org/wiki/Cellulose

Polysaccharide: glycogen



se (primarily al starch" – lant starch, ict. Broken juickly s.

Polysaccharide: chitin



 $(\beta 1-4 \text{ GlcNAc }\beta 1-4 \text{ GlcNAc})_n$

Among the most abundant of organic molecules on Earth. Main component of the cell walls of fungi and exoskeletons of arthropods such as insects and crustaceans





http://en.wikipedia.org/wiki/Chitin

Oligosaccharide comparative molecular diversity

	<u>Polypeptides</u>	<u>Glycans</u>
Building blocks	amino acids	monosaccharides
Number of different monomers	20 common	9 common
Linkage sites per monomer	1	3-4
Possible linkage configurations	1	2
Possible homodimer structures	1	6-8
Linkage modes	linear	linear or branched





Oligosaccharide comparative molecular diversity

Three different amino acids (Ala, Ser, Tyr) - 6 structures

Ala-Ser-Tyr Ala-Tyr-Ser Ser-Ala-Tyr Ser-Tyr-Ala Tyr-Ala-Ser Tyr-Ser-Ala

Three different sugars (Glc, Gal, Man) - 1,056 structures ...

Gal a1-2 Gic a1-2 Man a1- Gal a1-3 Gic a1-6 Man b1- Gal a1-4 Man b1-4 Gic a1-3 Gal a1- Man b1-3 Gal b1-2 Gic b1-2 Gal b1- Gic b1-4 Man a1-4 Gal a1- Gic b1-4 Man a1-4 Gal a1- Gic b1-4 Man a1-4 Gal a1- Gic b1-4 Man b1-3 Gal b1- Gic b1-4 Man b1-3 Gal b1-6 Gic b1-4 Man b1-4 Gic b1-4 Man b1-3 Gal b1-6 Gic b1-4 Man b1-3 Gal b1-6 Gic b1-4 Man b1-3 Gal b1-6 Gic b1-4 Man b1-4 Gic b1-4 Man b1-4 Gic b1-4 Man b1-3 Gal b1-6 Gic b1-4 Man b1-3 Gal b1-6 Gic b1-Gal a1-3 Gic a1-2 Man a1- Gal a1-4 Gic a1-5 Man b1-4 Gic a1-5 Man b1-4 Gic a1-3 Gal a1- Man b1-3 Gic b1-2 Gal b1- Man b1-4 Gal b1-5 Gic a1-2 Man b1-4 Gal a1-6 Man b1-4 Gal a1-6 Man b1-4 Gic a1-3 Man b1- Gal a1-6 Man b1-2 Gic a1-3 Gal a1-3 Man b1-2 Gic a1-3 Gic a1-4 (Man a1-6) Gal a1-Gal a1-4 Gic a1-2 Man a1- Gal a1-6 Gic a1-6 Man b1- Gal a1-6 Man b1-4 Gic b1-2 Gal b1- Man b1-4 Gic b1-2 Gal b1-6 Gic a1-6 Gic a1-2 Man a1-6 Gal a1-3 Man b1-4 Gal a1-3 Man b1-4 Gic b1-3 Man b1-4 Gic b1-2 Man b1-4 Gic b1-2 Man b1-6 Gic a1-2 Man a1-6 Gic a1-2 Man a1-6 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b1-2 Man b1- Gai b1-3 (Gic a1-4) Man b1- Gai a1-6 (Man a1-2) Gic b1- Gic a1-2 (Man a1-6) Gai b1-Three different sugars Gal a1-2 Gic b1-2 Man a1- Gal a1-3 Gic b1-6 Man b1 6 Glc b1 Glc Sic b1- Gic a1-3 (Man a1-2) Gal b1-Gal a1-3 Glc b1-2 Man a1-Gal a1-4 Glc b1-6 Man b1 6 Glc b1 Using the 9 monosaccharides of Glc b1- Glc a1-3 (Man a1-4) Gal b1-Man b1-6 Gal a1-3 Glc b1 6 Glc b1 Gic b1- Gic a1-3 (Man a1-6) Gal b1-Gal a1-4 Gic b1-2 Man a1- Gal a1-6 Gic b1-6 Man b1 Gal a1-6 Glc b1-2 Man a1- Gal b1-2 Glc b1-6 Man b1-2 Glc b1 Glc Glc b1- Glc a1-4 (Man a1-2) Gal b1-(Glc, Gal, Man) -Gal b1-2 Glc b1-2 Man a1-Gal b1-3 Glc b1-6 Man b1 2 Glc b1 human glycans, ~10¹² (one trillion)* Glc b1- Glc a1-4 (Man a1-3) Gal b1-Man a1-2 Gal a1-4 Glc b1 Gal b1-3 Glc b1-2 Man a1- Gal b1-4 Glc b1-6 Man b1-2 Glc b1 Glc b1- Glc a1-4 (Man a1-6) Gal b1-2 Glc b1 Gal b1-4 Glc b1-2 Man a1- Gal b1-6 Glc b1-6 Man b1 Glc b1- Glc a1-6 (Man a1-2) Gal b1-1,056 structures Gal b1-6 Glc b1-2 Man a1-Gal a1-2 Man a1-2 Glc at 2 Glc b1 Gic b1- Gic a1-6 (Man a1-3) Gal b1hexasaccharides can be drawn. Man a1-3 Gal a1-4 Glc b1 2 Glc b1 Gal a1-2 Gic b1-3 Man a1- Gal a1-3 Man a1-2 Gic a1 Gic b1- Gic a1-6 (Man a1-4) Gal b1-Gal a1-3 Glc b1-3 Man a1- Gal a1-4 Man a1-2 Glc a1-2 Glc b1 Gic b1- Gic b1-2 (Man a1-3) Gal b1 Gal a1-4 Glc b1-3 Man a1-Gal a1-6 Man a1-2 Gic a1 2 Glc b1 Gic b1- Gic b1-2 (Man a1-4) Gal b1-Why don't we quit now and work on Gal a1-6 Glc b1-3 Man a1- Gal b1-2 Man a1-2 Glc a1--3 Glc b1 Gic b1- Gic b1-2 (Man a1-6) Gal b1-Man a1-4 Gal a1-4 Glc b1 3 Glc b1 Gal b1-2 Glc b1-3 Man a1- Gal b1-3 Man a1-2 Glc a1 Glc b1- Glc b1-3 (Man a1-2) Gal b1-Gal b1-3 Glc b1-3 Man a1- Gal b1-4 Man a1-2 Glc a1 3 Glc b1 Glc b1- Glc b1-3 (Man a1-4) Gal b1 something else? Gal b1-4 Gic b1-3 Man a1- Gal b1-6 Man a1-2 Gic at -3 Glc b1 Gic b1- Gic b1-3 (Man a1-6) Gal b1-Man a1-6 Gal a1-4 Glc b1 Gal b1-6 Glc b1-3 Man a1- Gal a1-2 Man a1-3 Glc a1 3 Glc b1 Glc b1- Glc b1-4 (Man a1-2) Gal b1-Gal a1-2 Gic b1-4 Man a1- Gal a1-3 Man a1-3 Gic a1 3 Glc b1 Glc Gic b1- Gic b1-4 (Man a1-3) Gal b1 Gal a1-3 Glc b1-4 Man a1- Gal a1-4 Man a1-3 Glc a1-3 Glc b1 Glc Glc b1- Glc b1-4 (Man a1-6) Gal b1-Man b1-2 Gal a1-4 Glc b1 Gal a1-4 Gic b1-4 Man a1- Gal a1-6 Man a1-3 Gic a1 3 Glc b1 Glc Glc b1- Glc b1-6 (Man a1-2) Gal b1-Gal a1-6 Glc b1-4 Man a1-Gal b1-2 Man a1-3 Glc a1 4 Glc b1 Glc Glc b1- Glc b1-6 (Man a1-3) Gal b1-*Laine Glycobiology 4:759 (1994) 4 Glc b1 Glc Gic b1- Gic b1-6 (Man a1-4) Gal b1-Gai b1-2 Gic b1-4 Man a1- Gai b1-3 Man a1-3 Gic a1 Man b1-3 Gal a1-4 Glc b1 Gal b1-3 Glc b1-4 Man a1- Gal b1-4 Man a1-3 Glc a1 4 Glc b1 Glc Gic b1- Gic a1-2 (Man b1-3) Gal b1-Gal b1-4 Glc b1-4 Man a1-Gal b1-6 Man a1-3 Glc a1 4 Glc b1 Glc b1-2 Man a1-3 Gal b1-Glc b1-3 Gal b1-2 Man a1-Gic b1-4 Gal b1-6 Man b1- Gal b1-3 (Gic b1-2) Man b1- Gal a1-4 (Man b1-6) Gic b1- Gic a1-2 (Man b1-4) Gal b1-4 Glc b1 Gal b1-5 Glc b1-4 Man a1- Gal a1-2 Man a1-4 Glc a1-Glc b1-3 Man a1-3 Gal b1- Glc b1-4 Gal b1-2 Man a1- Glc b1-6 Gal b1-6 Man b1- Gal b1-3 (Glc b1-4) Man b1- Gal a1-6 (Man b1-2) Glc b1- Glc a1-2 (Man b1-6) Gal b1-Man b1-4 Gal a1-4 Glc b1 Gal a1-2 Gic b1-6 Man a1- Gal a1-3 Man a1-4 Gic a1 4 Glc b1 Glc b1-4 Man a1-3 Gal b1- Glc b1-6 Gal b1-2 Man a1- Gal a1-2 (Glc a1-3) Man a1- Gal b1-3 (Glc b1-6) Man b1- Gal a1-6 (Man b1-3) Glc b1- Glc a1-3 (Man b1-2) Gal b1-Gal a1-3 Glc b1-6 Man a1- Gal a1-4 Man a1-4 Glc a1 4 Glc b1 Glc b1-6 Man a1-3 Gal b1-Glc a1-2 Gal b1-3 Man a1-Gal a1-2 (Glc a1-4) Man a1- Gal b1-4 (Glc b1-2) Man b1- Gal a1-6 (Man b1-4) Glc b1- Glc a1-3 (Man b1-4) Gal b1-Gal a1-4 Gic b1-6 Man a1- Gal a1-6 Man a1-4 Gic a1 4 Glc b1 Glc a1-2 Man a1-4 Gal b1- Glc a1-3 Gal b1-3 Man a1- Gal a1-2 (Glc a1-6) Man a1- Gal b1-4 (Glc b1-3) Man b1- Gal b1-2 (Man b1-3) Glc b1- Glc a1-3 (Man b1-6) Gal b1-Gal a1-5 Glc b1-6 Man a1- Gal b1-2 Man a1-4 Glc a1 Man b1-6 Gal a1-4 Glc b1 6 Glc b1 Glc ai-3 Man ai-4 Gal bi- Glc ai-4 Gal bi-3 Man ai- Gal ai-3 (Glc ai-2) Man ai- Gal bi-4 (Glc bi-6) Man bi- Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man bi-2) Gal bi-2 (Man bi-4) Glc bi- Glc ai-4 (Man Gal b1-2 Glc b1-6 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Gai a1-4 (Gic a1-6) Man a1- Gai a1-2 (Man a1-4) Gic a1- Gai b1-4 (Man b1-2) Gic b1- Gic a1-6 (Man b1-4) Gai b1-Gal a1-3 Glc a1-2 Man b1-Gal a1-4 Man a1-6 Glc a1 6 Glc b1 Glc b1-6 Man a1-4 Gal b1- Glc a1-2 Gal b1-4 Man a1-Gal a1-6 (Gic a1-2) Man a1- Gal a1-2 (Man a1-6) Gic a1- Gal b1-4 (Man b1-3) Gic b1- Gic b1-2 (Man b1-3) Gal b1-Man a1-3 Gal a1-6 Glc b1 Gal a1-4 Glc a1-2 Man b1-Gal a1-6 Man a1-6 Glc a1 6 Glc b1 Glc a1-2 Man a1-6 Gal b1-Gic a1-3 Gal b1-4 Man a1-Gal a1-6 (Gic a1-3) Man a1- Gal a1-3 (Man a1-2) Gic a1- Gal b1-4 (Man b1-6) Gic b1- Gic b1-2 (Man b1-4) Gal b1-2 Gal a1- Gic a1-3 Man a1-6 Gal b1- Gic a1-4 Gal b1-4 Man a1- Gal a1-6 (Gic a1-4) Man a1- Gal a1-3 (Man a1-4) Gic a1- Gal b1-6 (Man b1-2) Gic b1-2 (Man b1-6) Gal b1-6 (Man b1-7) Gic b1-2 (Man b1-7) Gic b1-7 (Ma Gal a1-5 Glc a1-2 Man b1- Gal b1-2 Man a1-5 Glc a1 Gal b1-2 Glc a1-2 Man b1- Gal b1-3 Man a1-6 Glc a1-2 Gal a1- Glc a1-4 Man a1-6 Gal b1-Glc a1-6 Gal b1-4 Man a1-Gal b1-2 (Gic a1-3) Man a1- Gal a1-3 (Man a1-6) 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b1-6 Gal b1-3 Glc a1-Gic a1-2 Man a1-3 Gal a1-Glc a1-3 Man b1-2 Gal b1-Glc a1-4 Gal b1-6 Man a1-Gal b1-4 (Glc a1-3) Man a1- Gal b1-2 (Man a1-3) Glc a1- Glc a1-3 (Man a1-6) Gal a1- Glc b1-6 (Man b1-3) Gal b1-Man a1-2 Gai b1-4 Gic a1- Gic a1-3 Man a1-3 Gai a1- Gic a1-4 Man b1-2 Gai b1- Gic a1-6 Gai b1-6 Man a1-Gal b1-2 Glc a1-3 Man b1-Gal b1-3 Man b1-2 Glc a1-Gal b1-4 Man b1-6 Glc b1-Man b1-6 Glc a1-4 Gal b1-Gal b1-4 (Gic a1-6) Man a1- Gal b1-2 (Man a1-4) Gic a1- Gic a1-4 (Man a1-2) Gal a1- Gic b1-6 (Man b1-4) Gal b1-Gal b1-3 Glc a1-3 Man b1-Gal b1-4 Man b1-2 Glc a1-Gal b1-6 Man b1-6 Glc b1-Man a1-2 Glc a1-6 Gal b1-Man a1-3 Gal b1-4 Glc a1-Gic a1-4 Man a1-3 Gal a1- Gic a1-6 Man b1-2 Gal b1- Gic b1-2 Gal b1-6 Man a1-Gal b1-6 (Gic a1-2) Man a1- Gal b1-2 (Man a1-6) Gic a1- Gic a1-4 (Man a1-3) Gal a1-Gal b1-4 Glc a1-3 Man b1-Gal b1-6 Man b1-2 Glc a1-Man a1-2 Glc a1-2 Gal a1-Man a1-3 Glc a1-6 Gal b1-Man a1-4 Gal b1-4 Glc a1-Gic a1-6 Man a1-3 Gal a1- Gic b1-2 Man b1-2 Gal b1- Gic b1-3 Gal b1-6 Man a1-Gal b1-6 (Gic a1-3) Man a1- Gal b1-3 (Man a1-2) Gic a1- Gic a1-4 (Man a1-6) Gal a1-Gal b1-6 Glc a1-3 Man b1- Gal a1-2 Man b1-3 Glc a1-2 Gal a1- Man a1-4 Glc a1-5 Gal b1- Man a1-4 Glc a1-6 Gal b1-4 Glc b1-2 Man a1-3 Gal a1- Glc b1-2 Man b1-2 Gal b1-6 [Man b1-2 Gal b1-6 [Man a1-3 Gal a1- Glc b1-4 Glc b1-4 Glc b1-4 Gal b1-6 [Man a1-4 Glc b1-4 Glc b Gal a1-2 Glc a1-4 Man b1-Gal a1-3 Man b1-3 Glc a1-Man a1-4 Gic a1-2 Gal a1- Man a1-6 Gic a1-6 Gal b1- Man b1-2 Gal b1-4 Gic a1- Gic b1-3 Man a1-3 Gal a1- Gic b1-4 Man b1-2 Gal b1- Gic b1-6 Gal b1-6 Man a1-Gal a1-2 (Glc b1-3) Man a1- Gal b1-3 (Man a1-6) Glc a1- Glc a1-6 (Man a1-3) Gal a1-Gal a1-3 Glc a1-4 Man b1-Gal a1-4 Man b1-3 Glc a1-Man a1-6 Glc a1-2 Gal a1-Man b1-2 Glc a1-6 Gal b1-Man b1-3 Gal b1-4 Glc a1-Gic b1-4 Man a1-3 Gal a1- Gic b1-6 Man b1-2 Gal b1-Glc a1-2 Gal a1-2 Man b1-Gal a1-2 (Glc b1-4) Man a1- Gal b1-4 (Man a1-2) Glc a1- Glc a1-6 (Man a1-4) Gal a1-Gal a1-4 Gic a1-4 Man b1- Gal a1-6 Man b1-3 Gic a1-2 Man b1-2 Gic a1-2 Gal a1- Man b1-3 Gic a1-6 Gal b1- Man b1-4 Gic a1-6 Gic b1-6 Man a1-3 Gal a1- Gic a1-2 Man b1-3 Gal a1-2 Man b1-3 Gic a1-2 Man b1-4 Gic a1-Gal a1-2 (Gic b1-6) Man a1- Gal b1-4 (Man a1-3) Gic a1- Gic b1-2 (Man a1-3) Gal a1-Gal a1-6 Glc a1-4 Man b1-Gal b1-2 Man b1-3 Glc a1- Man b1-3 Glc a1-2 Gal a1- Man b1-4 Glc a1-6 Gal b1- Man b1-6 Gal b1-4 Glc a1- Glc a1-2 Man a1-4 Gal a1- Glc a1-3 Man b1-3 Gal b1- Glc a1-4 Gal a1-2 Man b1-Gal a1-3 (Glc b1-2) Man a1- Gal b1-4 (Man a1-6) Glc a1- Glc b1-2 (Man a1-4) Gal a1-Gal b1-2 Glc a1-4 Man b1-Gal b1-3 Man b1-3 Glc a1- Man b1-4 Glc a1-2 Gal a1- Man b1-6 Glc a1-6 Gal b1-Man a1-2 Gal b1-6 Glc a1- Glc a1-3 Man a1-4 Gal a1- Glc a1-4 Man b1-3 Gal b1- Glc a1-6 Gal a1-2 Man b1-Gal a1-3 (Glc b1-4) Man a1- Gal b1-6 (Man a1-2) Glc a1- Glc b1-2 (Man a1-6) Gal a1-Gal b1-3 Glc a1-4 Man b1- Gal b1-4 Man b1-3 Glc a1- Man b1-5 Glc a1-2 Gal a1- Man a1-2 Glc b1-2 Gal b1- Man a1-3 Gal b1-6 Glc a1-4 Man a1-4 Gal a1- Glc a1-6 Man b1-3 Gal b1- Glc b1-2 Gal a1-2 Man b1- Glc a1-3 [Man a1-3 Glc b1-2 Gal a1-6 [Man a1-3] Glc a1-7 [Man a1-3] [Man a1-7 [Man a1-3] [Man a1-3] [Man a1-3] [Man a1-3] [Man a1-3] [Man a1 Gal b1-4 G(c a1-4 Man b1- Gal b1-5 Man b1-3 G(c a1- Man a1-2 G(c a1-3 Gal a1- Man a1-3 G(c b1-2 Gal b1- 6 (C a1-4 G(c a1-6 Man a1-4) G(c a1-6 Man Gal b1-6 Gic a1-4 Man b1- Gal a1-2 Man b1-4 Gic a1-2 Man b1-4 Gic a1-3 Gal a1-2 Man a1-4 Gic b1-2 Gal b1-6 Gic a1- Gic b1-3 Gal a1-4 Gic b1-3 (Man a1-6) Gal a1-6 Gic a1-4 Man b1-3 Gal a1-6 Gic a1-4 Man b1-3 Gal a1-2 Man b1-3 Gal Gal a1-2 Gic a1-6 Man b1- Gal a1-3 Man b1-4 Gic a1-3 Gal a1- Man a1-6 Gic b1-2 Gal b1- Man b1-2 Gal b1-6 Gic a1- Gic b1-3 Man a1-4 Gal a1- Gic b1-4 Man b1-3 Gal b1- Gic b1-6 Gal a1-2 Man b1-4 Gic a1-3 Gal a1-2 (Man b1-4) Gic a1- Gic b1-4 (Man a1-2) Gal a1-

Glycan diversity is biosynthetically constrained and analytically tractable

- 209 human glycosyltransferases
- ~3,000 glycoprotein and glycolipid "glycan determinants"
- ~4,000 proteoglycan pentasaccharide determinants



The Glycobiology Landscape: Sugars as language

- Glycans: the "missing mass" of the biological universe
- Monosaccharides: The alphabet of glycoscience
- The glycosidic bond and glycan nomenclature
- Major carbohydrate classes: sugars, polysaccharides, oligosaccharides and glycans
- Major glycans of mammals

- Glycoproteins
 - N-linked
 - **O-linked**
 - **GPI**-anchored
 - **O-GIcNAc**





N-linked glycoprotein glycans



Families of N-linked glycan structures



With terminal saccharide diversity

Neu5Ac α 2-6 Gal β 1-4 GlcNAc---

Neu5Ac α 2-3 Gal β 1-4 GlcNAc---

Gal α1-3 Gal β1-4 GlcNAc---

4-SO₃-GalNAc β 1-4 GlcNAc---

 $(-Gal \beta 1-4 GlcNAc \beta 1-3-)_n = polylactosamine repeats (n may be >9)$

 $(-\text{Neu5Ac }\alpha 2-8-)_n = \text{polysialic acid (n may be >50)}$

Fuc residues (e.g. Fuc α 1-2 Gal; Fuc α 1-3 GlcNAc; Fuc α 1-4 GlcNAc)

Terminal Saccharide Diversity is key to molecular recognition

O-linked glycoprotein glycans



O-linked glycan structures







- Glycoproteins
 - N-linked
 - **O-linked** •
 - **GPI**-anchored
 - **O-GIcNAc**





Glycophosphatidylinositol (GPI) anchor







Note: No further sugar substitutions have been confirmed Highly dynamic post-translational modification!

- Glycoproteins
- Glycolipids
- Proteoglycans











Neu5Ac



Glc

- Glycoproteins
- Glycolipids
- Proteoglycans





Glycosaminoglycans & Proteoglycans

- GLYCOSAMINOGLYCANS (GAG's)
 - long linear glycans made of characteristic repeating disaccharides
 - hyaluronic acid is the only "stand-alone" GAG, other GAG's are constituents of ...
- PROTEOGLYCANS
 - GAG's on proteins
 - Defined by their repeating disaccharide units
 - GAG's on proteoglycans are sulfated

Hyaluronic acid a space filling & signaling molecule





(GlcU β4 GlcNAc)_n



globular protein (MW 50,000) glycogen (MW ~ 400,000) spectrin (MW 460,000) collagen (MW 290,000) hyaluronan (MW 8 x 10⁶) 300 nm

Proteoglcans -masters of post-polymerization modifications



Proteoglycans - masters of molecular complexing





Principles of glycan biosynthesis

- Activated nucleotide sugar donors
- >200 glycosyltransferases (human genome)



UDP-Gal:glucose β 4 galactosyltransferase

Activated Sugars: UDP-Glc UDP-GlcA UDP-Gal UDP-Xyl GDP-Man GDP-Fuc UDP-GlcNAc CMP-NeuAc UDP-GalNAc
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Modes of glycan biosynthesis

- Glycoproteins
 - N-Linked en-bloc preconstructed core, trimming, terminal elaboration
 - O-Linked stepwise sugar by sugar addition
 - O-GlcNAc dynamic transferase/glycosidase
 - GPI Anchor en-bloc preconstructed core, elaboration
- Glycolipids
 - Stepwise sugar-by-sugar addition
- Proteoglycans
 - Stepwise sugar-by-sugar addition (core and repeating dissaccharide)
 - Post-polymerization modifications

- Glycoproteins
- Glycolipids
- Proteoglycans



