

# A World of Sugars: From Sugars in Space to Daily Life

Serge Perez, Firenze, Ottobre 2016

1



## Sucrose

*Sugar cane : was discovered in New Guinea, arrived to India around 600 BC and reached Persia when Darius invaded India. Upon invading Spain, Arabs brought sugar to Europe around 700 AD.*

*Etymology : sanskrit "SARKARA" (grain), translated as sukkar in arabic, saccharum in latin and zucchero in italian*

**Western Europe : average consumption 25 kg of sucrose par year per capita**

Disaccharide  
D-glucopyranose  
D-fructofuranose

*Sugar beat : identified by a German Chemist, Andreas Marggraf en 1747; and brought to culture under Napoleon on the occasion of the british blockade.*

Production of 145 millions tons/year of a « molecularly » pure product !

## What do we mean by « Sugars » ?

Refer to a vast family of molecules, which are **homogeneous** ( $C_x (H_2O)_y$ ) and **diversified**.

Made up of **Carbone, Hydrogen & Oxygen**.

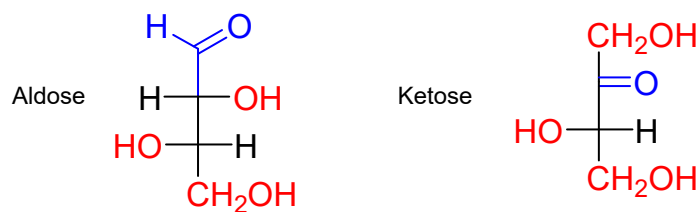
They are referred to as « **Carbohydrates** », « **Hydrates de carbone** » « **Kohlenhydrate** » but also « **Saccharides** » and « **Glycans** »

**Oligosaccharides, Polysaccharides**

**Glycoconjugates as in Glycopeptides, Glycoproteins, Glycolipids**

## Molecular Diversity of Monosaccharides

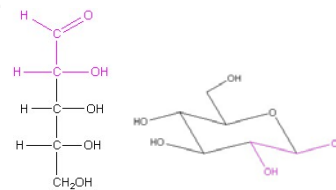
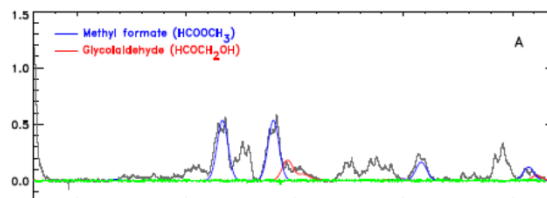
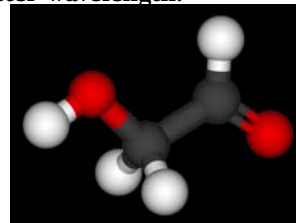
- Carbon chain (3 à 10 Carbons) multiforms
- All Carbons are functionalized
- Coexistence of a **Carbonyl group** (aldehyde or ketone) with several (2 to 9) **Hydroxyl groups** : aldoses / ketoses
- Dual character **Electrophile – Nucleophile**



## Sugar in Space

(400 light-years away to Earth)

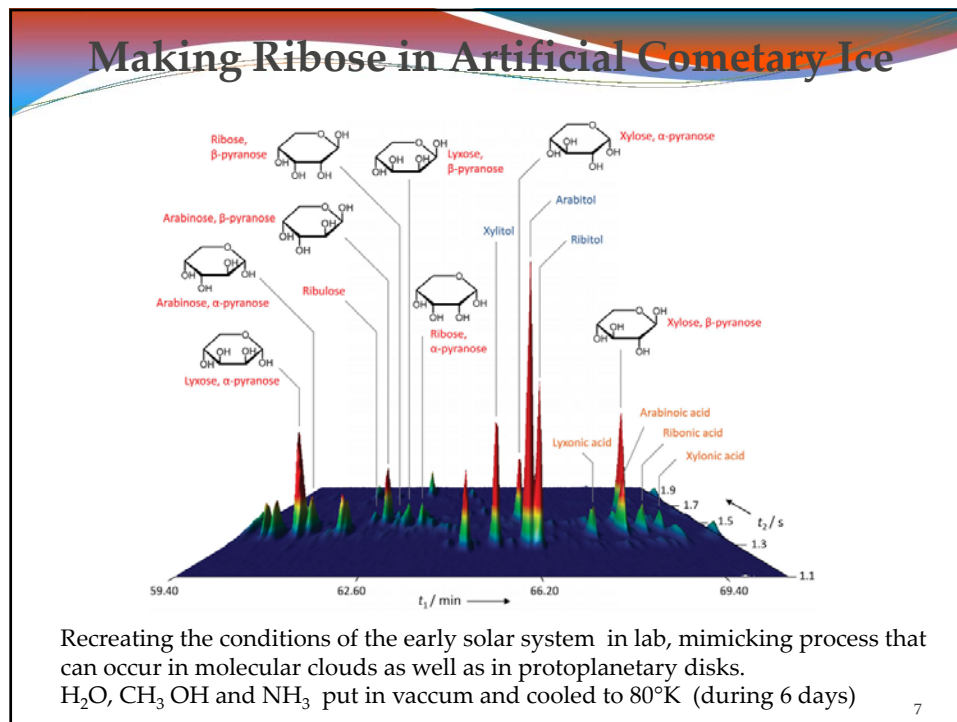
**Glycolaldehyde** (and its reduced alcohol variant – ethylene glycol) have been identified from the energy it emits as it changes its rotational energy level by absorbing and emitting in the millimeter wavelength.



**Ribose → ARN → ADN**

Jørgensen, J. K.; Favre, C.; Bisschop, S.; Bourke, T.; Dishoeck, E.; Schmalzl, M. (2012). Detection of the simplest sugar, glycolaldehyde, in a solar-type protostar with ALMA ([http://www.eso.org/public/archives/releases/science\\_papers/es01234/es01234a.pdf](http://www.eso.org/public/archives/releases/science_papers/es01234/es01234a.pdf))

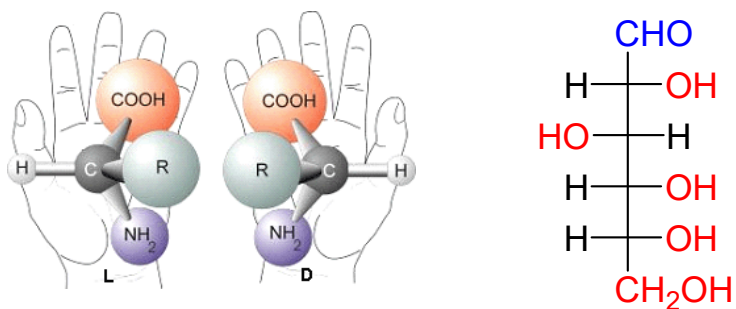
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## Molecular Diversity of Monosaccharides

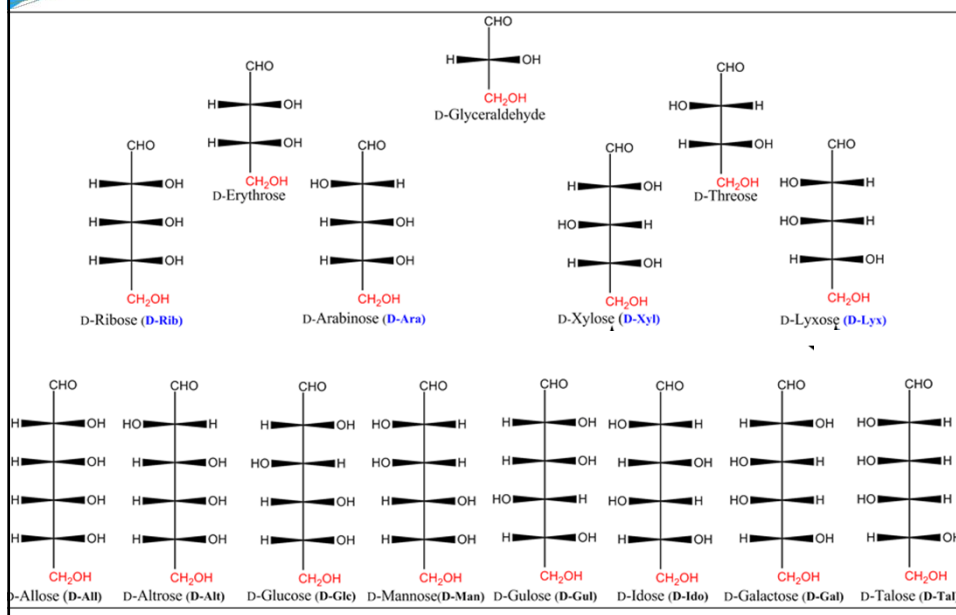
- **Heteroatoms** – Nitrogen, Sulphur – may introduce other functionalities and enrich the corresponding sub families: glycosylamines, thiosugars, glucosinolates ...
- **Oxidized forms:** uloses, glycaric acids, glyconics, glycuronics ...
- **Reduced forms:** deoxy-sugars, itols ...
- **Unsaturated variants** : enoses, glycals ...

## Chirality & Stereochemistry



9

## Historical Representation of Monosaccharides

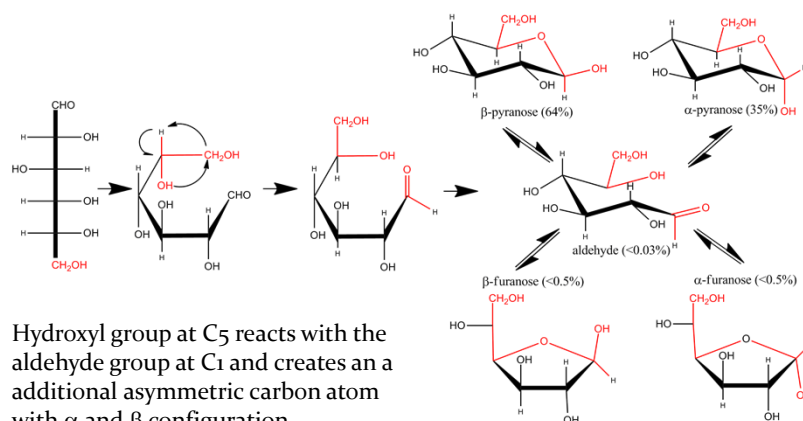


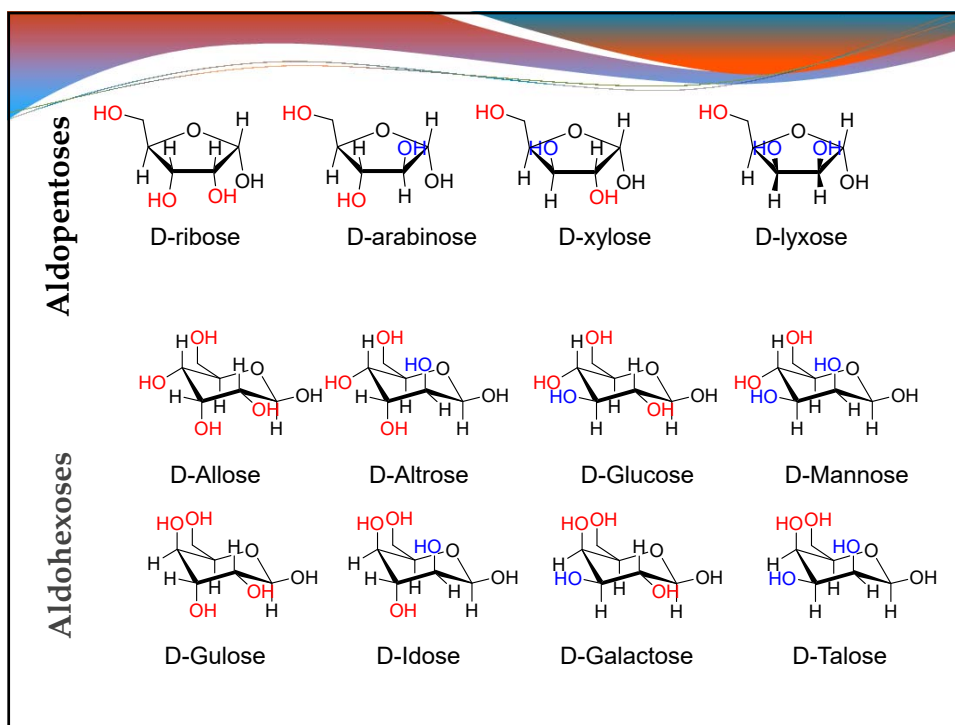
## Equilibrium Chain - Ring

- There exists an **equilibrium** (reversible or not) between the linear chains and the cyclic form. Its formation is favored under weak acidic or alkaline conditions).
- The more stable rings are (4C & 1 O) (**furanose**) and (5C & 1O) (**pyranose**).
- Ring locking generates a crucial supplementary complexity: **the anomeric carbon: with two configurations.**

either  $\alpha$ , or  $\beta$

## Mutarotation : Configurational Equilibrium





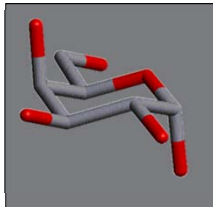
**Evolution of the Depiction of Monosaccharides**


Fischer assigned the dextrorotatory glucose (via glucaric acid) the projection with the OH group at C5 pointing to the right. But the absolute configuration was established in 1951 (Bijvoet) by X-ray crystallography

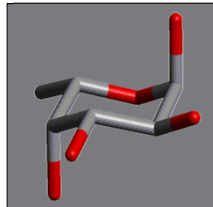
14

## Conformational Complexity

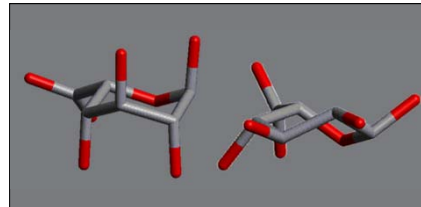
- The most common rings are furanoid or pyranoid, with five and six members.
- Furanose ring structures occur in Envelope (E) and Twist (T) conformations.
- Six membered ring structures can occur in 2 chairs (C), 6 boat (B), 6 Skew (S) and 12 half-chair (H) conformations.
- These conformations result in orientating in space the different functions of the monosaccharide, which have an impact on recognition and reactivity.



D-Glucose



L-Fucose



L-iduronic Acid

## The Isomer Barrier

Nucleotides	Peptides	Glycans
4 bases	20 amino acids	> 150 (700) monosaccharides
Linear	Linear	Lineare or branchéed
2 sites linkage	4 sites linkage	5 sites linkage With 2 stéreo-chemistr ( $\alpha / \beta$ )
<b>Hexanucleotide</b> $4^6 = 4096$	<b>Hexapeptide</b> $20^6 = 64\,000\,000$	<b>Hexasaccharide</b> 192 780 943 360 (with 10 monosaccharides)

### High Coding Capacity of Glycans

R. A. Laine, Glycobiology, 4, 759-767 (1994)

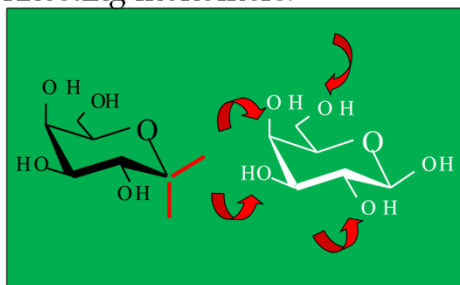
P. H. Seeberger, ACS Chem Biol, 2, 685-691 (2007)

16



## The Isomer Barrier

- Have a very high number of monomers (substitution...).
- Have many different ways of connecting monomers.
- Have branching points.
- Are difficult to synthesise ... and to crystallize.
- Are not the direct product of a gene ( $\neq$  proteins).
- Cannot be amplified by PCR ( $\neq$  Nucleic acids).



17

## A New and Complex Alphabet

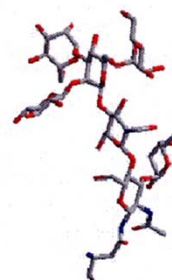
English

东 東

...TTGCCTAGTGATTGGATG...

...LysProSerAspTrpMet...

"Hemoglobin"



"I am a cancer cell"

**BioInformatics:** Difficulty to encode the structures

18

## Oligosaccharides & Polysaccharides

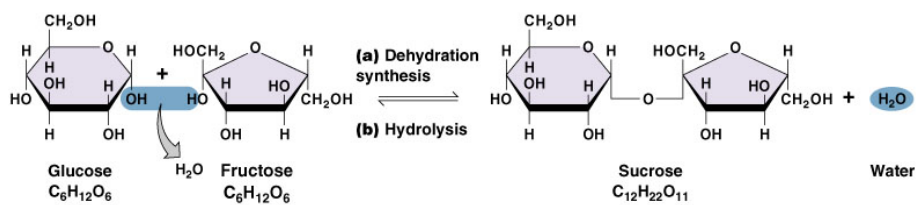
**Structural Complexity  
and  
Functional Diversity**

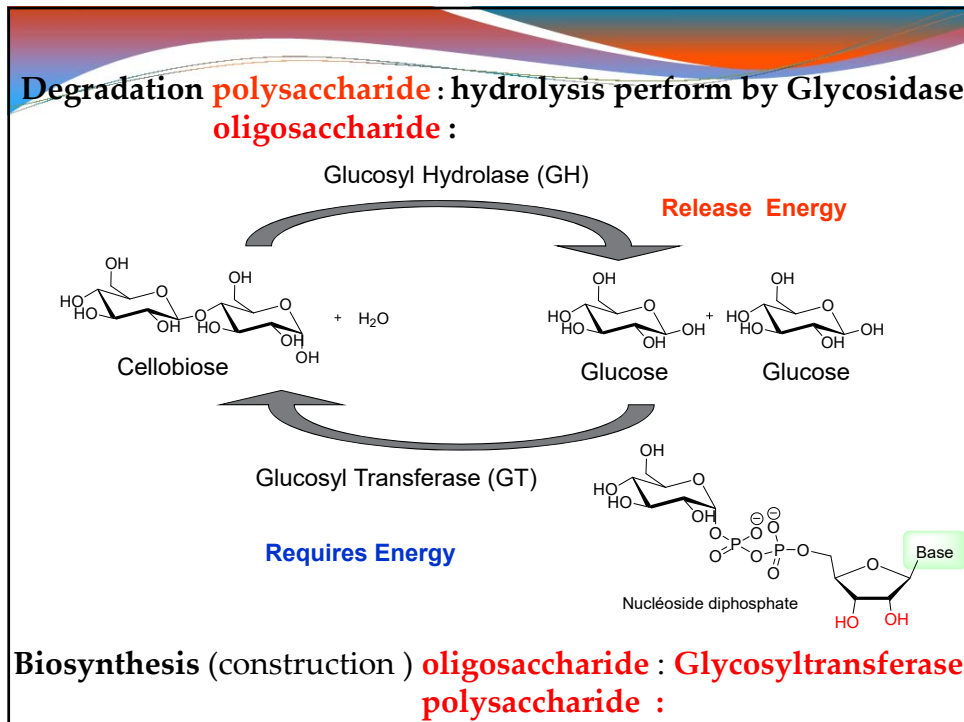


## Oligo & Polysaccharides :

Monosaccharide units linked by glycosidic linkage

One of the most stable linkage among those occurring in bio(macro)molecules





## Major Functions Played by Polysaccharides

**Energy Stores**

What manner of armor is this?!?

heh heh... EXOSKELETON!

**Structural support**

**Cellulose**

**Plasticity**

smooth region    hairy region    smooth region

■ galacturonic acid    ■ fucose    ○ galactose    ● arabinose

**Blood clot**

**Solution properties of physiological fluids**

**Extra-cellular matrix build-up**

Keratan sulfate  
Chondroitin sulfate  
Core protein  
Link protein  
Hyaluronic acid

2.2

## Starch


**Amylose :**  
Linear chain of glucoses linked  $\alpha 1,4$

**Amylopectin**  
Combination of amylose + branched linked  $\alpha 1,6$  glycosidic bonds

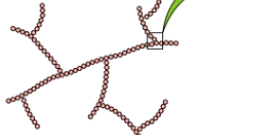
**Glycogen**  
some similarity to amylopectin  
but different types of branches

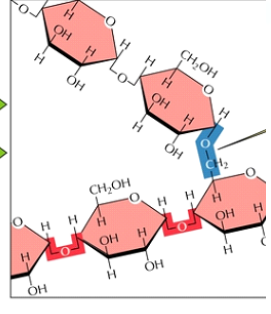
**Energy Storage**  
**Polymers of Glucose**

**Amylopectin (starch)**



**Glycogen**






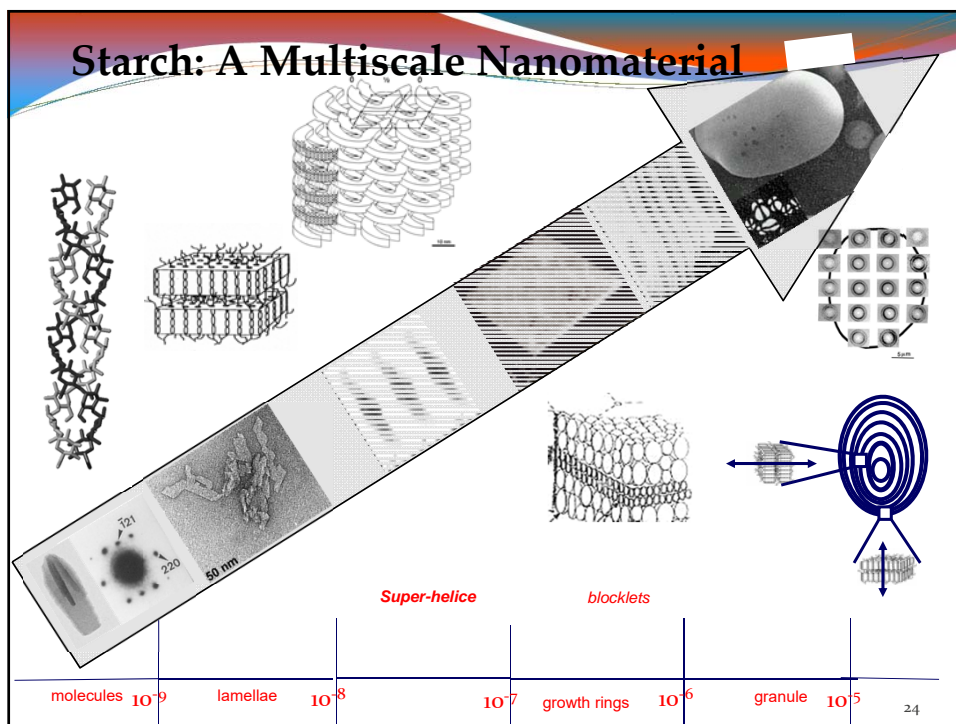


Figure 8-10.  $\alpha$ -Amylose.  
[Figure copyrighted © by Irving Geis.]  
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## Starch: A Multiscale Nanomaterial



**Super-helice**

**blocklets**

molecules	$10^{-9}$	lamellae	$10^{-8}$	$10^{-7}$	growth rings	$10^{-6}$	granule	$10^{-5}$
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24

## Other Energy Storage Polysaccharides,

(with linear structures more rare, found in plants and small animals)

**galactans** (in snails) ; 20-30 units

**fructane** (plants) 20-30 units



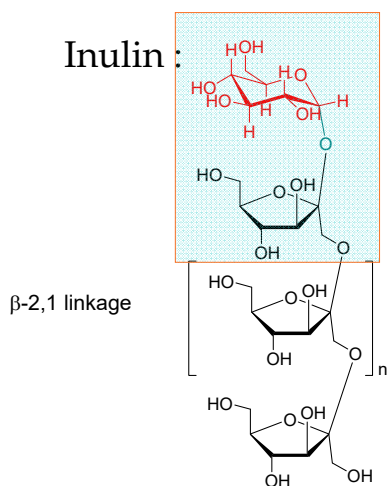
*Helianthus tuberosus*

Jerusalem artichoke  
Topinambour  
Topinanbur  
(carciofo di Gerusalemme)

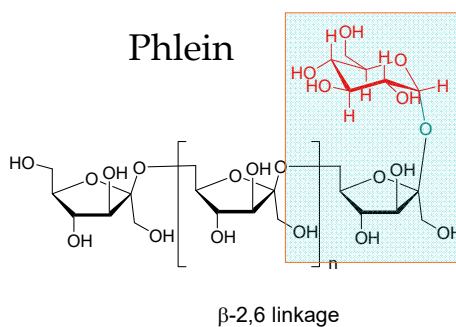
## Fructans : Two Types of Structures :

Inulin Phlein types

Inulin :



Phlein



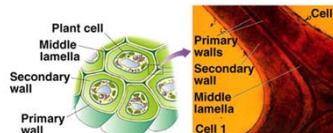
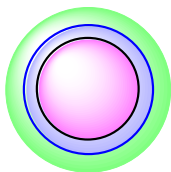
Phlein biosynthesized by phlein sucrose.  
High correlation of the chain length of  
phlein with the stress resistance.

## Structural Polysaccharides:

Highly diverse from micro-organisms to « higher organisms ».

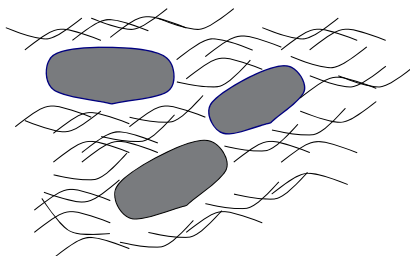
Bring mechanical stability and protection to bacterial, plants and animals.

Bacteria



Plants

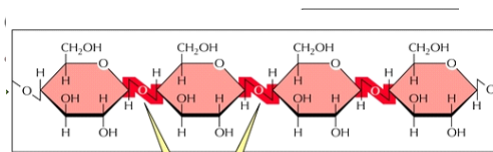
Animals



## Cellulose:

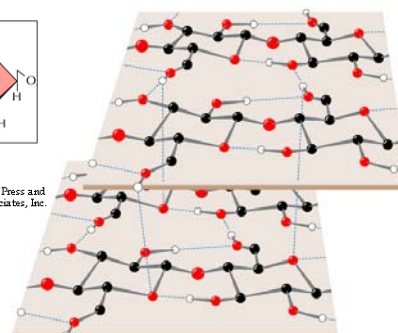
### Major Structural Constituents in Plants,.....

Cellulose:  
Linear chains of  $\beta$ 1,4 linked Glucose



Residues are joined by  $\beta$  (1-4) bonds.

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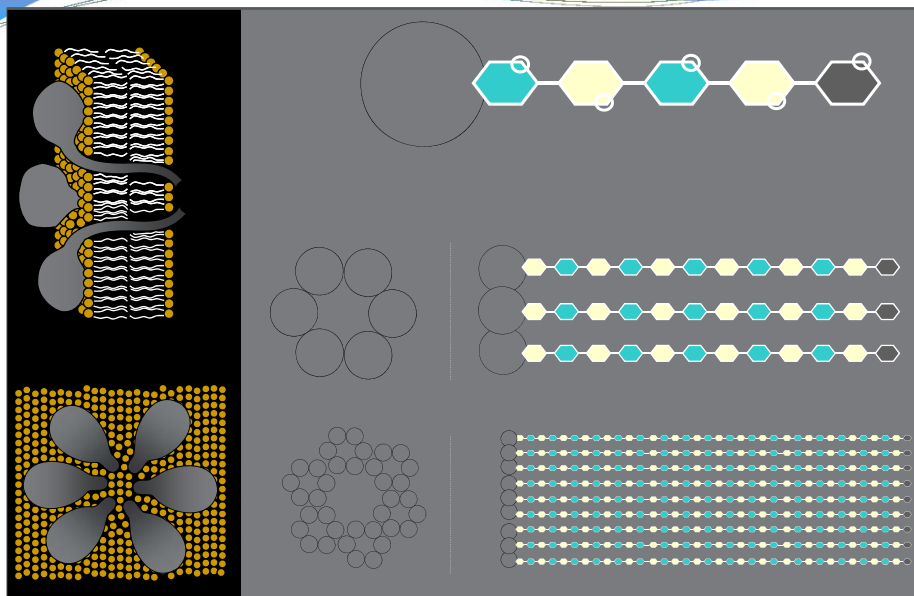


## Cellulose: Several Levels of Structural Organizations



29

## Cellulose Biosynthesis



300-1000 Glucose residues per minute (speed: 300 nm/min)

30

## Pectins

**Legend:**

- GalA
- Rha
- ▨ Dha
- GlcA
- ⊙ Fuc
- AcMeFuc
- ▲ AcAce
- Gal
- ▲ Ara
- KDO
- ▲ Api
- ◆ MeXyl
- △ Xyl
- ⊙ M Methyl
- A Acetyl

## Algae

Anionic polysaccharides - Gel forming (hydrocolloids)  
: Agar & Carrageenan, Alginates.

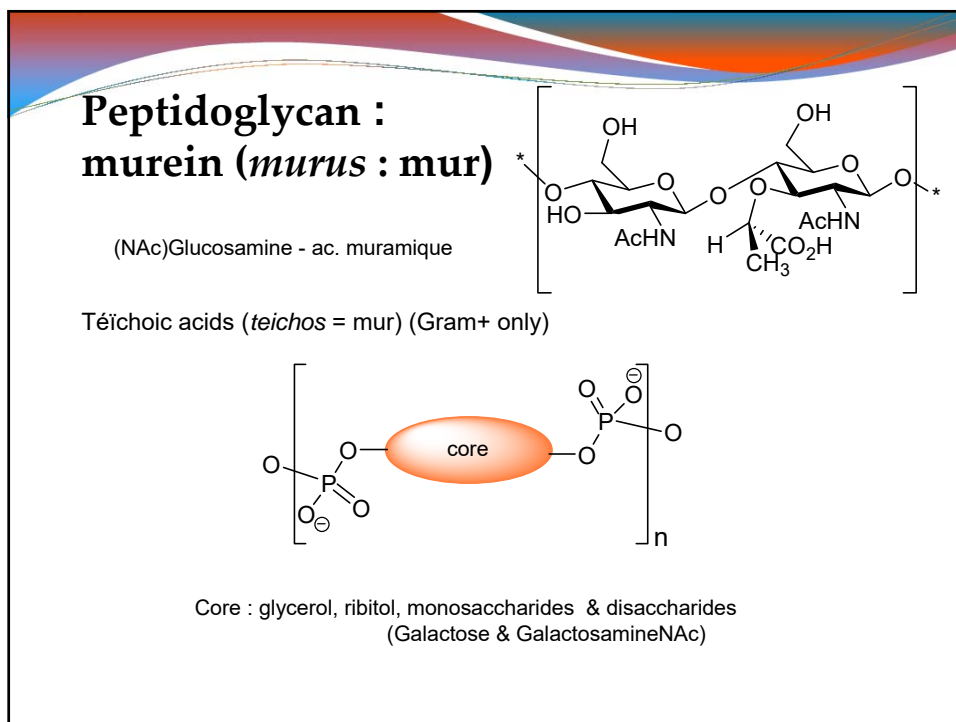
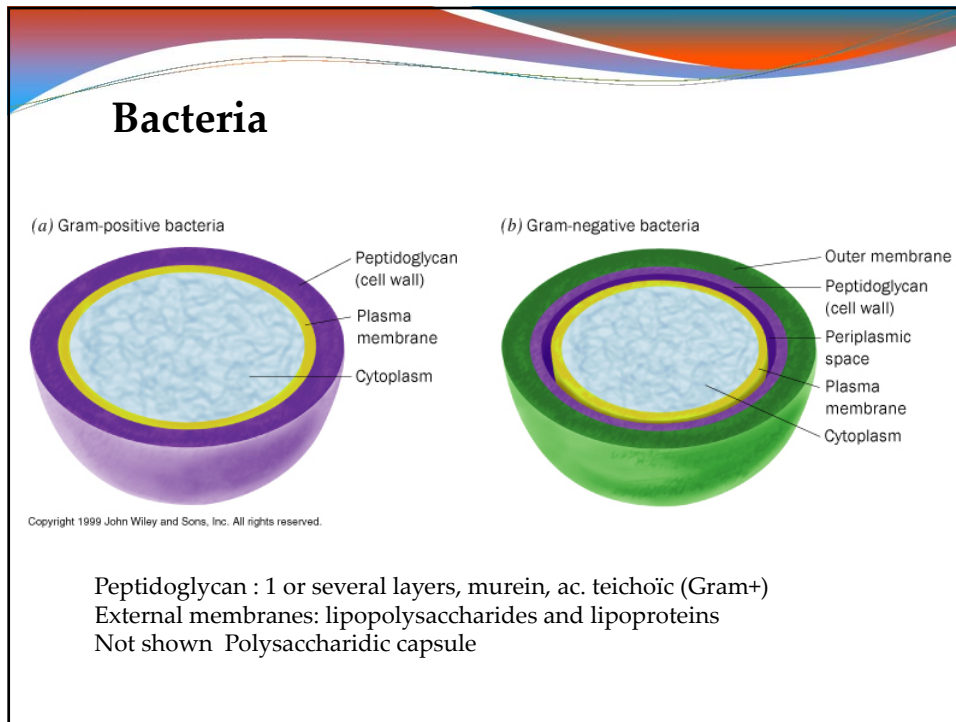
**Agar et Carrageenan**  
distributed in the cell walls of red algae : **galactans** et **mannans** . Made up Mannose a Sulfated galactose.

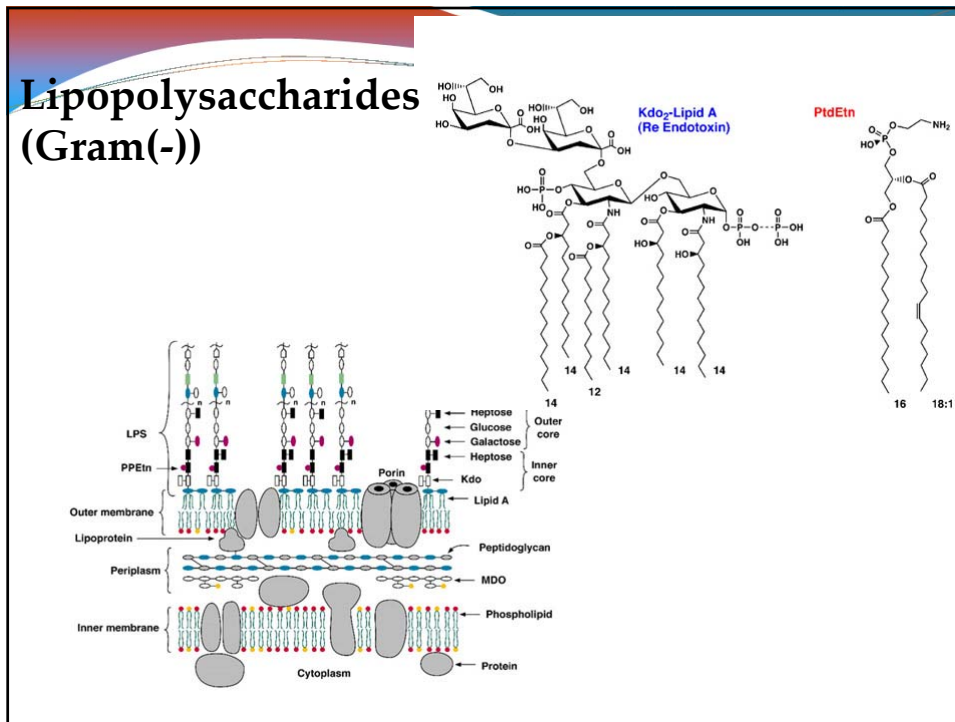
Modifications and variable patterns of sulfatations

**Alginate**, distributed widely in the cell walls of brown algae

Linear polysaccharides with Mannuronic & Guluronic







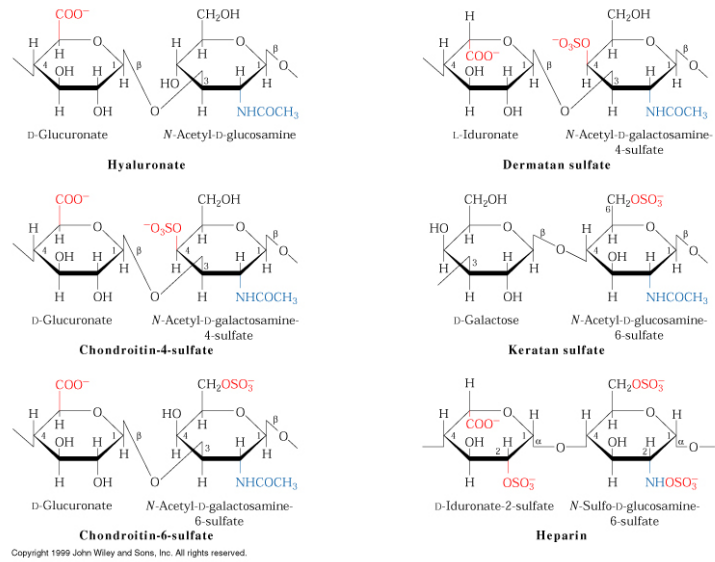
## Animals Glycosaminoglycans (GAGs)

- Linear polysaccharides: Uronic acid and Hexosamines
- High viscosity ; elasticity
- **Connective tissues, intercellular space (cartilages)**

The diagram illustrates the structure of Glycosaminoglycans (GAGs) and their location in animal connective tissues. The chemical structure shows a protein core with attached Keratan Sulfate, Chondroitin Sulfate, and Hyaluronic Acid. Link proteins are also shown connecting the GAGs to the protein core.

The diagram also shows a cross-section of cartilage with Type II Collagen Fibers, Chondrocytes, and Proteoglycans.

## Glycosaminoglycans GAGs :



## Oligosaccharides

4 to 10 monosaccharide units, usually as a result of the degradation or transformation of polysaccharides.

**α-Dextrins**

**FructoOligoSaccharides (FOS)**

**GalactoOligoSaccharides (GOS)**

**Cyclodextrines**

## Cyclodextrins : ( $\alpha$ , $\beta$ , $\gamma$ )

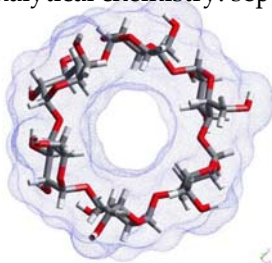
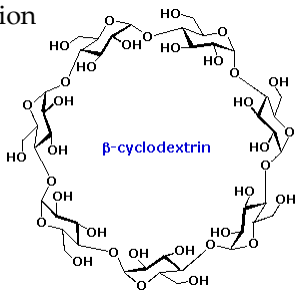

Cyclic Oligomers of  $\alpha$ 1-4 linked 6,7,8 Glucoses

Encapsulation

Enhance stability, solubility, controlled release, masking odor



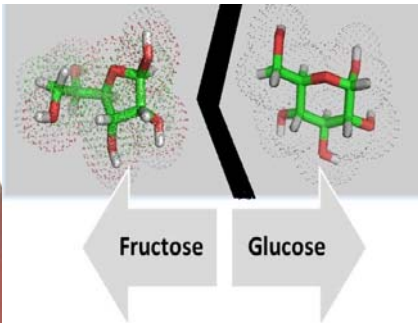
Applications: Pharmaceutical, Cosmetics, Food

Analytical chemistry: separation

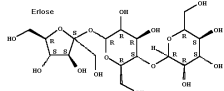
## Honey Oligosaccharides

### Honey Crystallization

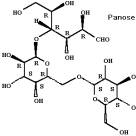




**F**  
as  
**Fructose & Fat**

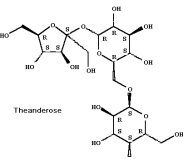
Eniose



Panose

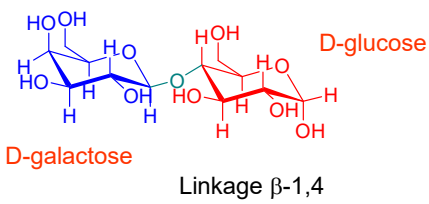


Theandrose




## The Most Common Disaccharides

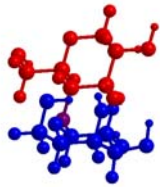
**Lactose** (galactose – glucose)





D-galactose      D-glucose

Linkage  $\beta$ -1,4





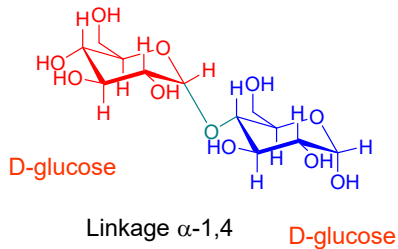




**Human Milk Oligosaccharides .....**


## The Most Common Disaccharides

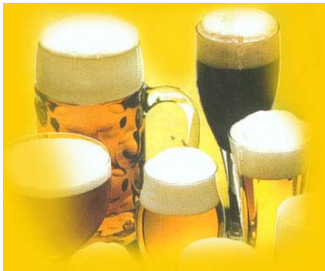
**Maltose** (glucose-glucose)

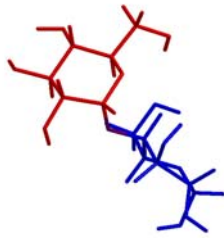


D-glucose      D-glucose

Linkage  $\alpha$ -1,4

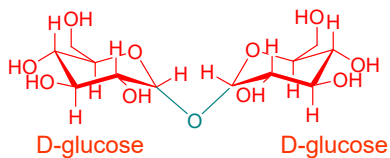




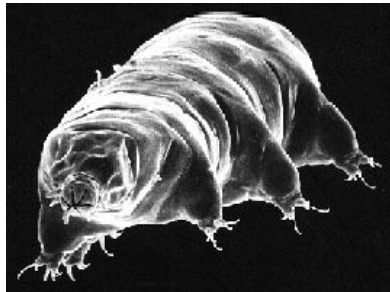


## The Most Common Disaccharides

### Trehalose (glucose-glucose)



Linkage  $\alpha$ -1,1



### Cryoprotection

Medical Applications :  
Stabilization & Protection  
antibodies, **enzymes**, embryos,  
help in transplantation  
...cosmetic

Cryoprotection- Tardigrades


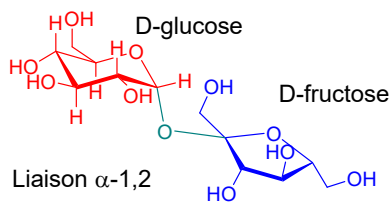


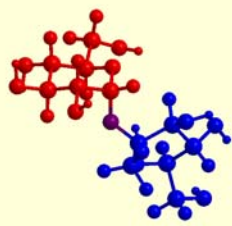
photo by H. Greven, Düsseldorf



## The Most Common Disaccharides

### Sucrose (glucose-fructose)




Liaison  $\alpha$ -1,2



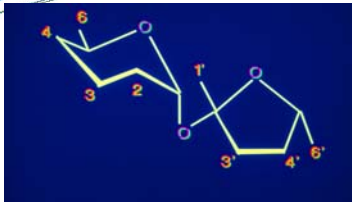
Sugar beat



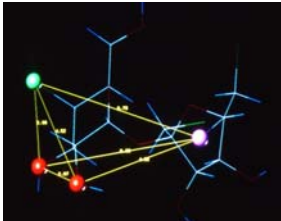
Sugar cane




## Sucrochemistry.....



2	3	4	6	1'	3'	4'	6'	Sw
-	-	Cl	Cl	Cl	-	-	Cl	100
-	-	Cl	Cl	Cl	-	-	Cl	200
-	-	Cl	-	Cl	-	Cl	Cl	2200
-	-	Cl	-	Cl	-	Cl	Cl	200
Cl	-	-	Cl	Cl	-	-	Cl	bitter
-	-	Br	-	Br	-	Br	Br	7500
-	-	Cl	H	Cl	-	-	Cl	400
-	-	Cl	OMe	Cl	-	-	Cl	500
-	-	Cl	OiPr	Cl	-	-	Cl	0
-	-	Cl	-	Cl	-	F	Cl	1000
-	-	Cl	-	Cl	-	Br	Cl	3000
-	-	Cl	-	Cl	-	I	Cl	3500
-	-	F	-	Cl	-	Cl	Cl	200
-	-	Br	-	Br	-	Br	Br	7000





## Du rêve à la réalité

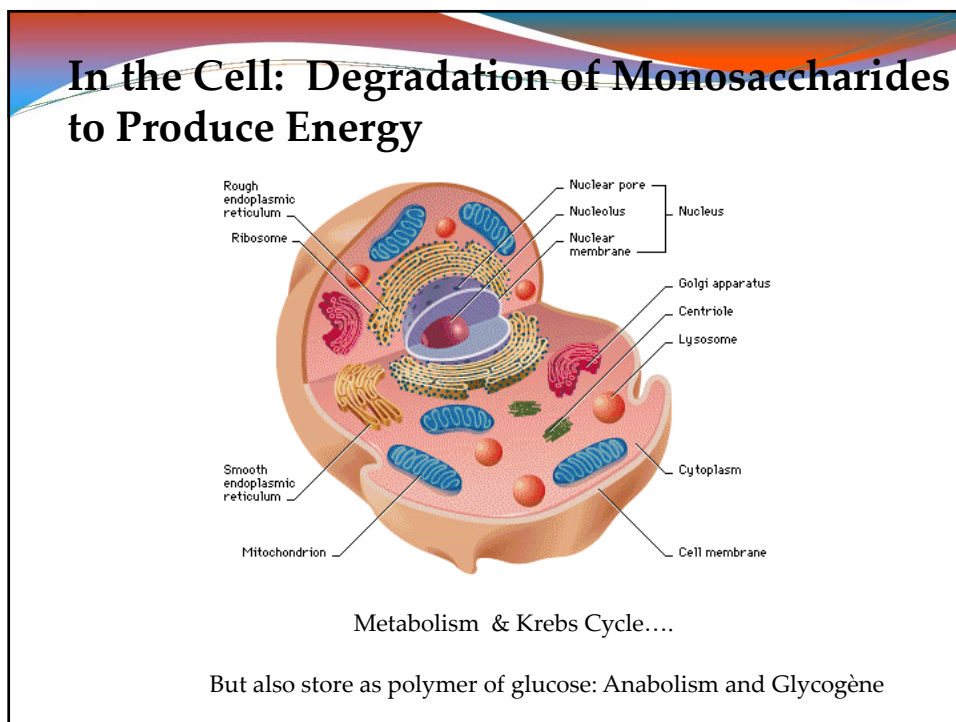
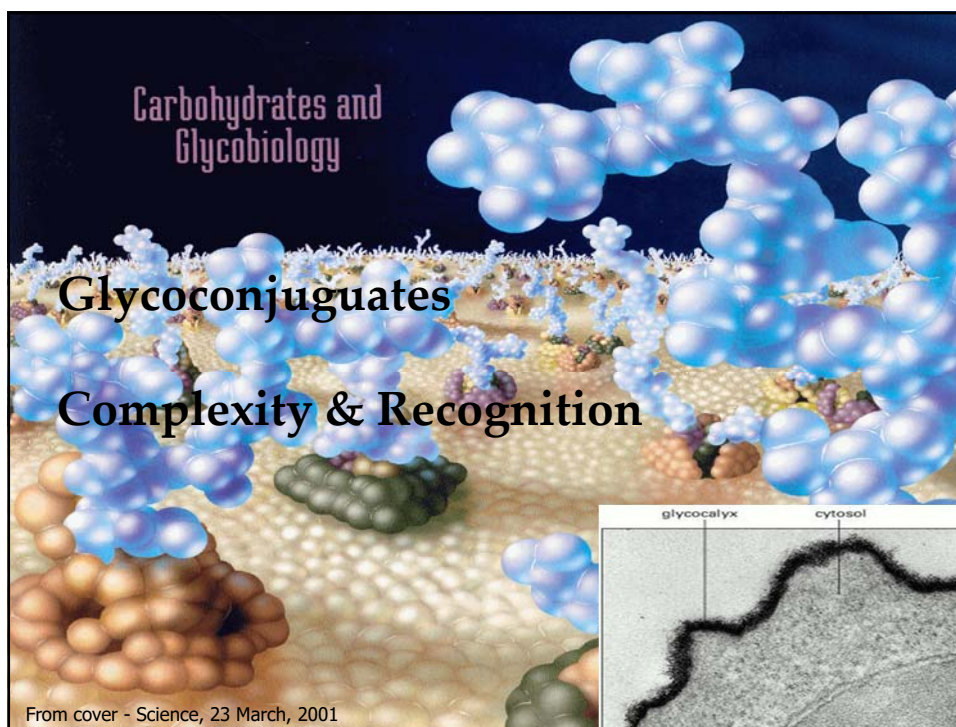




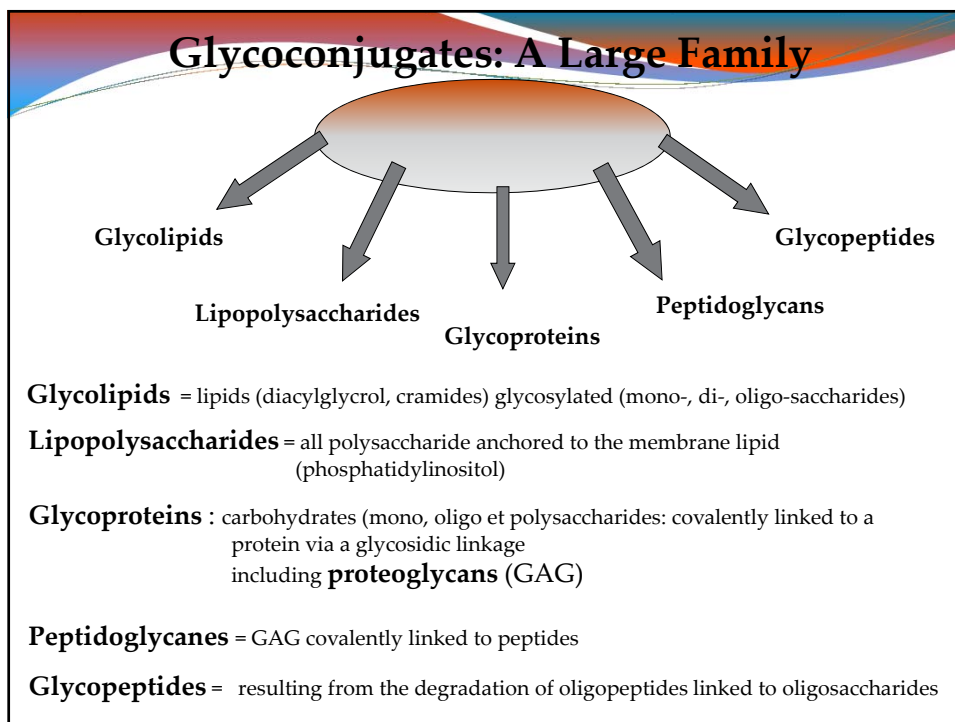
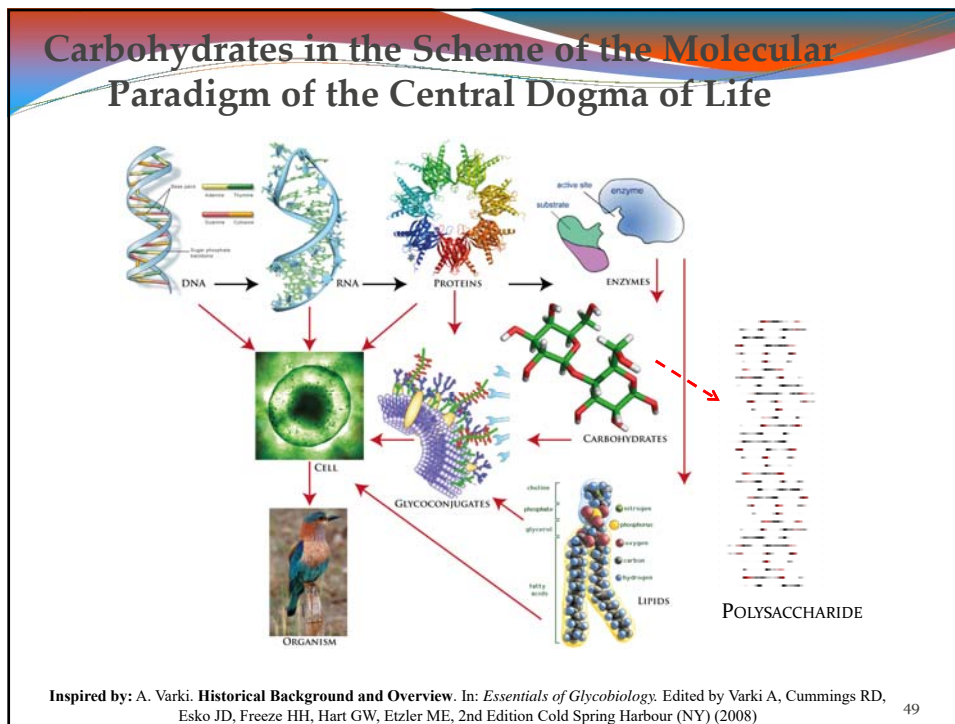




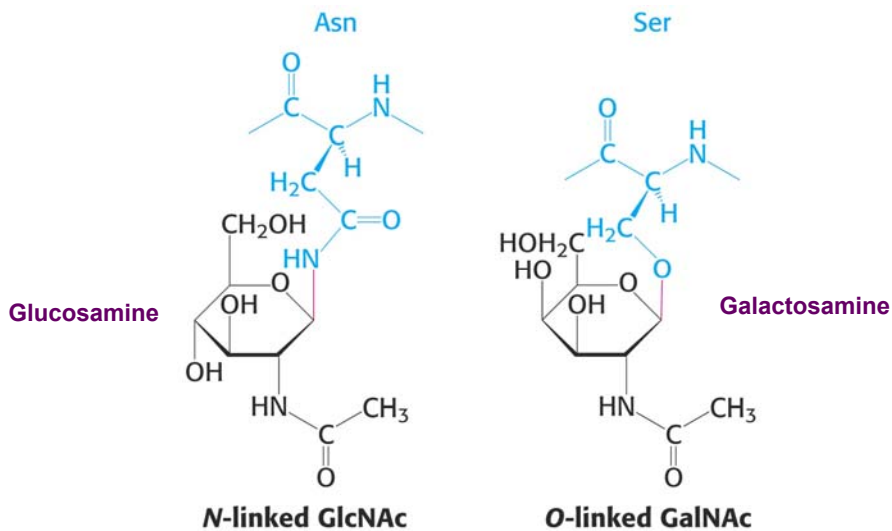
46



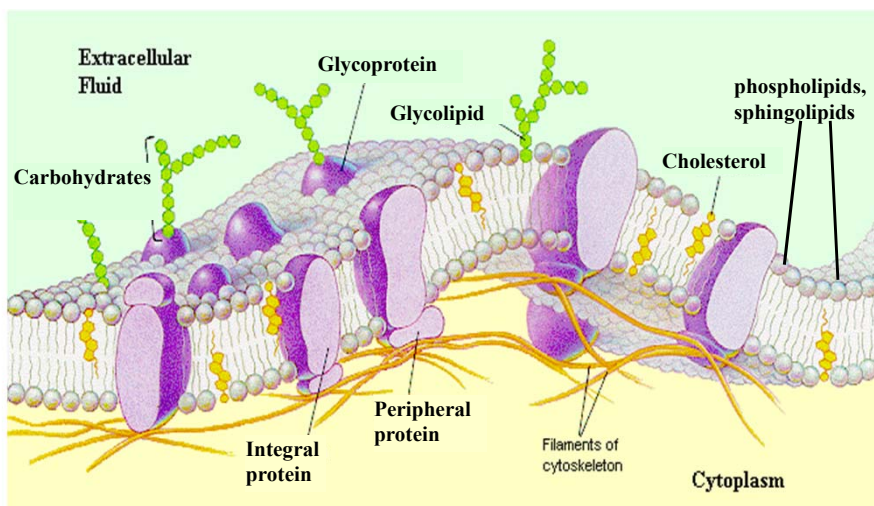


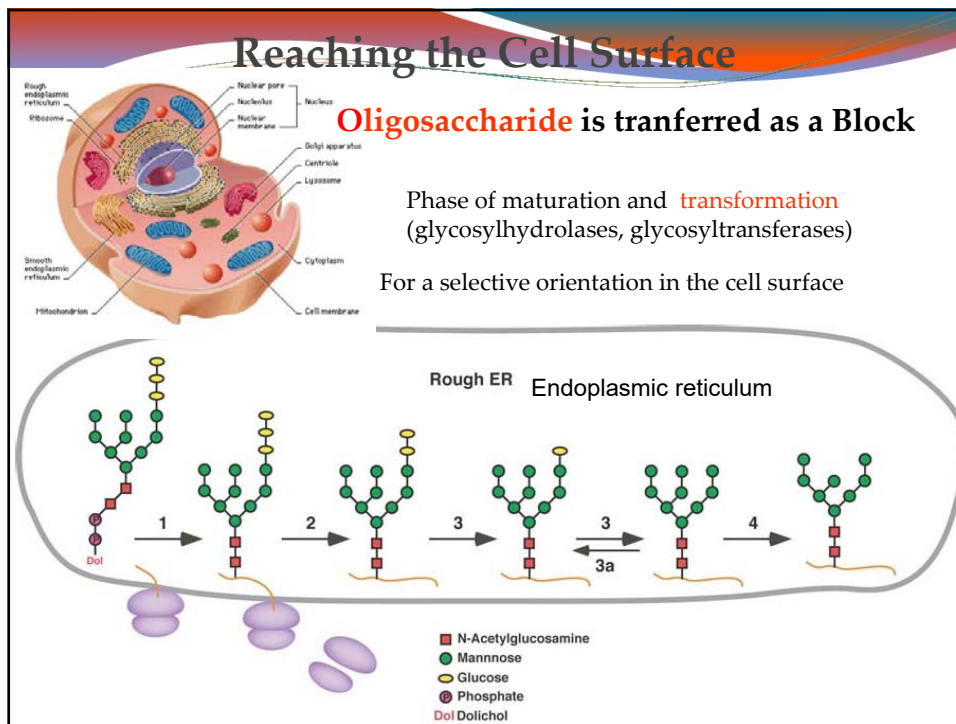


**For Proteins, 2 Types of Linkage  
N-linked (Asparagine) , O-linked (Serine)**



**Glycoconjugates:  
How do they get to the surface?**





## Glycoproteins

- Most of the extracellular proteins are glycosylated
- (N-linked or O-linked)
- Glycan provides
  - Stability
  - Solubility
  - Epitope masking
  - Interactions-recognition

## Oligosaccharides and Glycoconjugates

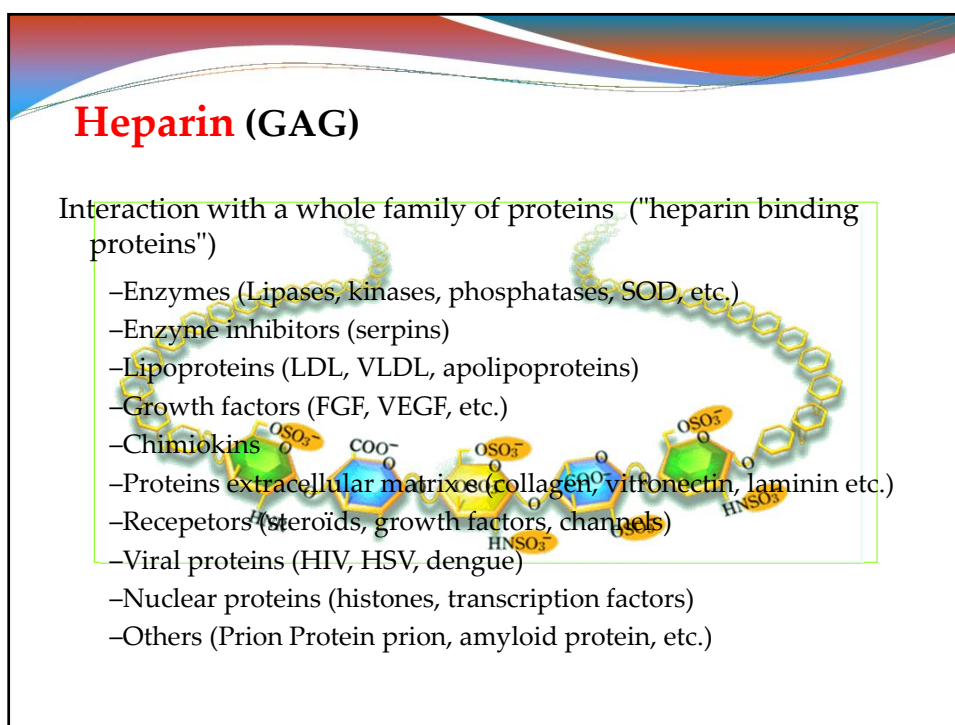
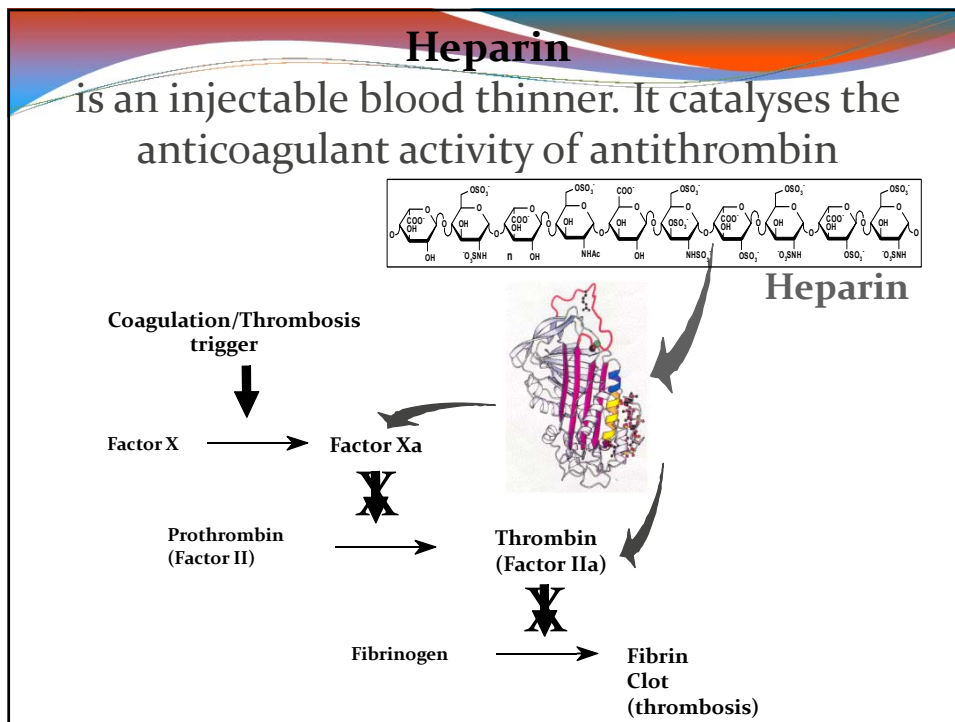
In living cells, glycans can be analogized to identity badges containing access codes to cells and/or cellular organelles.

55

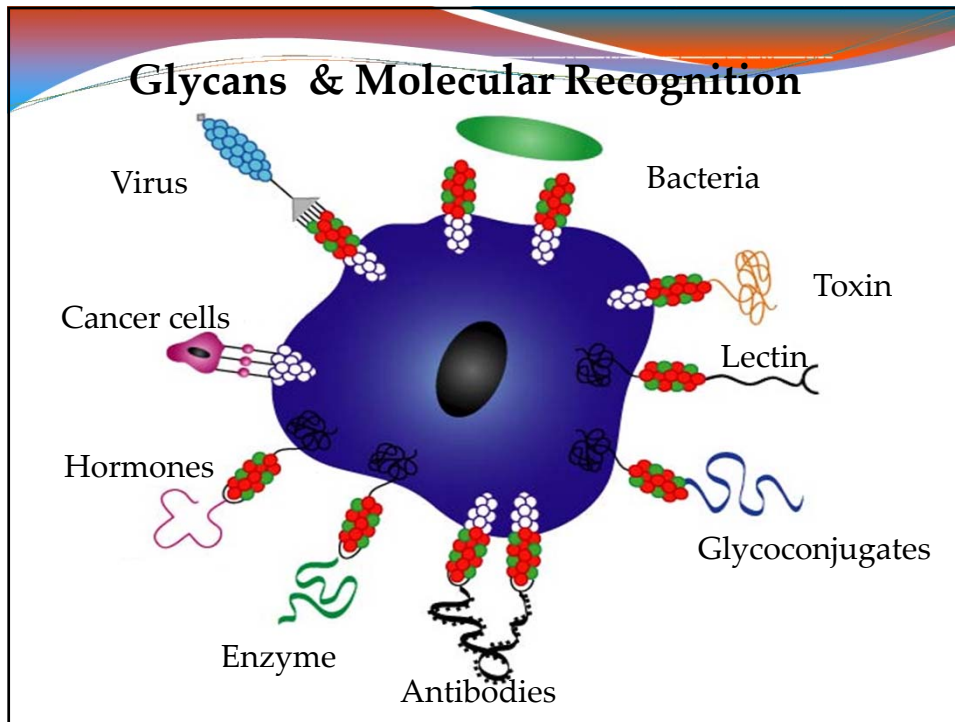
## The ProteoGlycans

**“Core protein”** with one or more covalently attached glycosaminoglycans (GAGs) : **occur in the connective tissue Extracellular matrix.**

- Chondroitin sulfate
- Keratan sulfate
- Dermatan sulfate
- Hyaluronic acid
- Heparin/Heparan sulfate





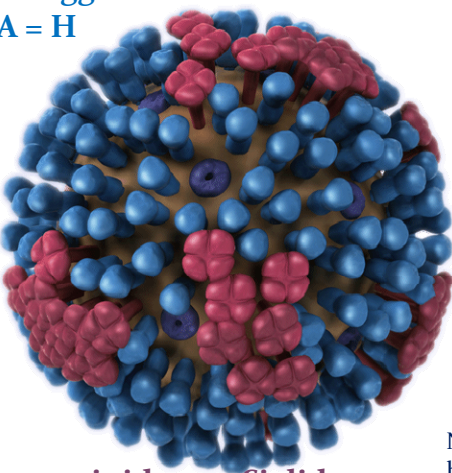


### Flu Virus & Glycans

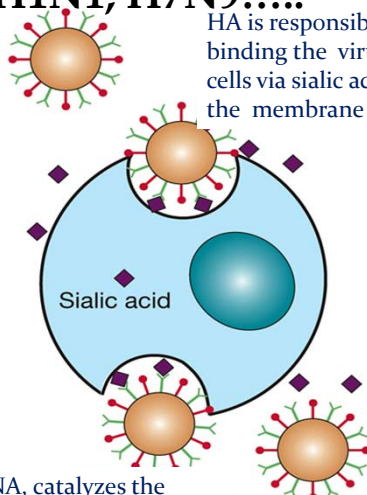
**World Health Organization:**  
A recent study estimated that world wide, annual influenza epidemics result in approximately **3 to 5 millions serious health cases and accounts to 250 000 to 500 000 deaths yearly.**

**The viral strain are called according to the Surface Proteins: H1N1, H7N9.....**

**Hemagglutinin**  
HA = H



HA is responsible for binding the virus to cells via sialic acid on the membrane



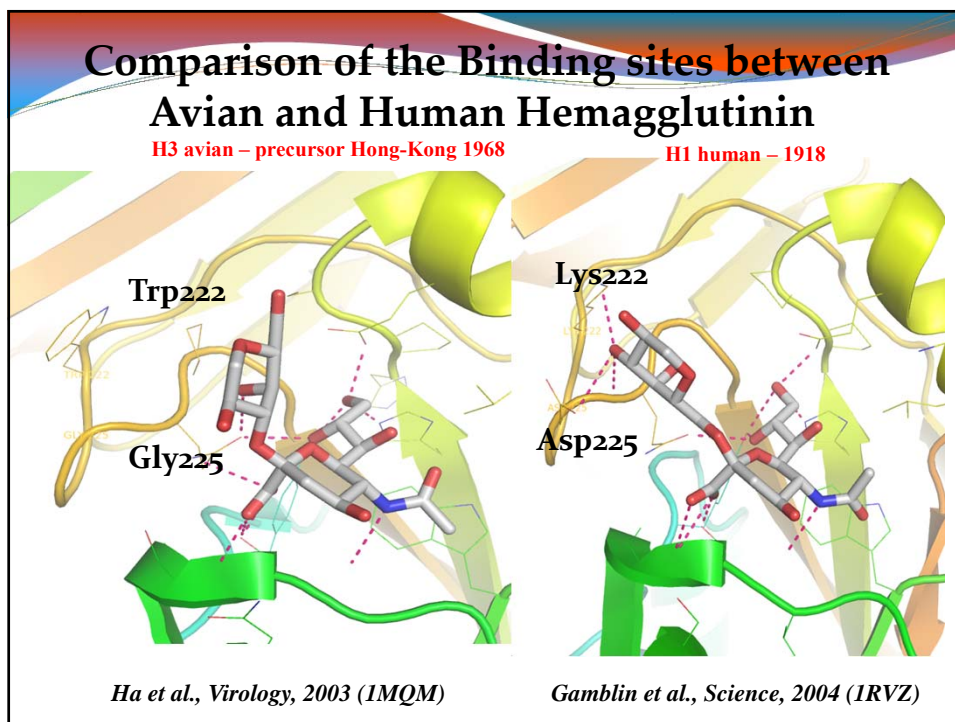
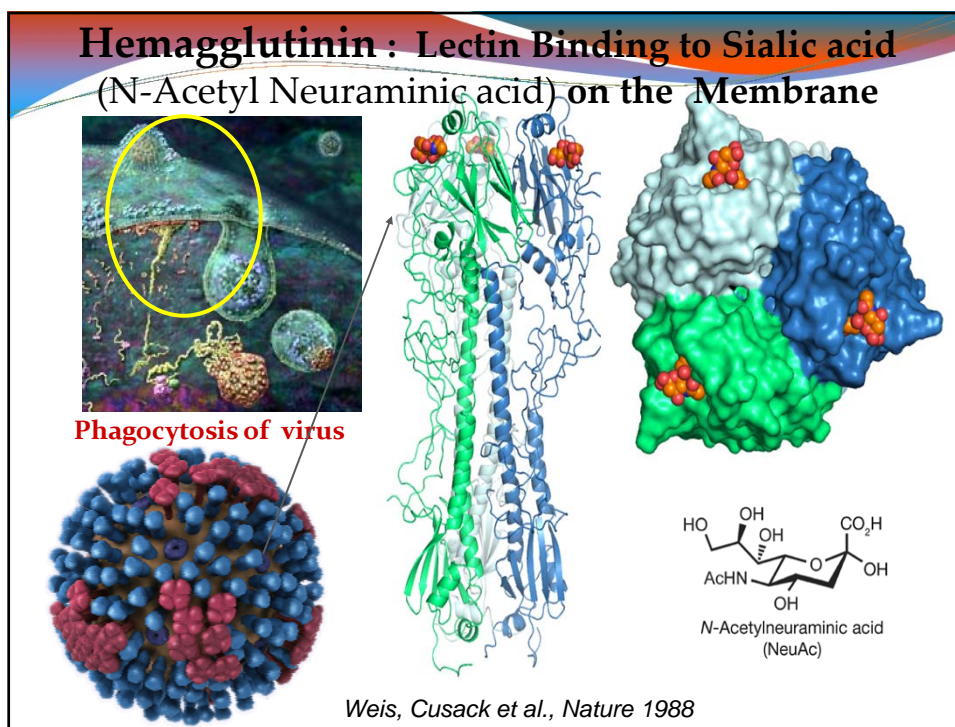
**Neuraminidase = Sialidase:**  
NA = N

NA, catalyzes the hydrolysis of sialic acid and allows budding and release

CDC : Center for Disease Control and Prevention    Essentials of Glycobiology, 2nd edition


**H: Hemaglutinine**  
**N: Neuraminidase**

Adapted from D. Mccandless

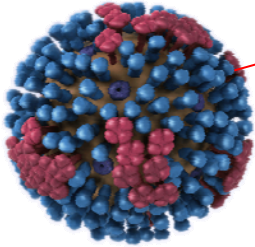


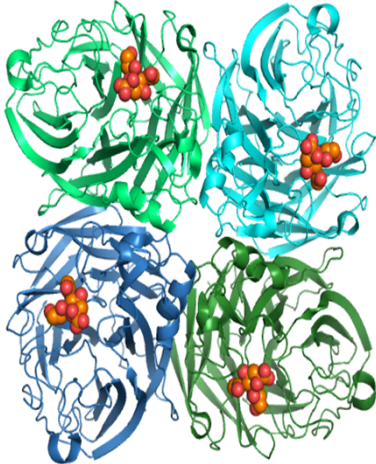


### Neuraminidase : Cleaves Sialic acid on our Cells



**Exocytosis of virus**

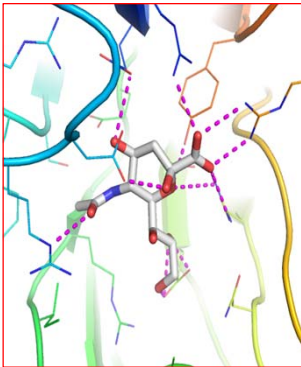
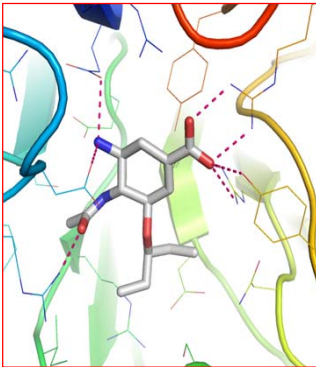
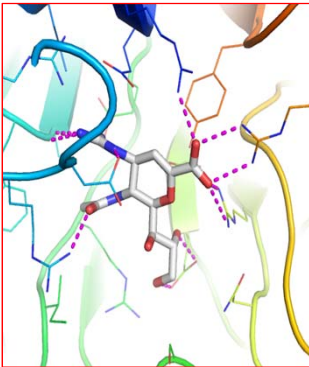




CC(=O)N[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O1

N-Acetylneuraminic acid  
(NeuAc)

### Conception of Neuraminidase (N1) Inhibitors Leading to Drugs

N1 with sialic Acid	N1 / oseltamivir (Tamiflu)	N1 / anamivir (Relenza)
		
<i>Varghese et al., Proteins 1992</i>	<i>Russel et al., Nature 2006</i>	<i>Wu et al., J. Virol. 2008</i>

## Oligosaccharides as Antigen Determinants

<b>Tn: Antigen</b> GalNac-Ser	<b>Tumor cells markers</b>
<b>Tf Antigen</b> Gal $\beta$ 1-3 GalNac - Ser	<b>Tumor cells markers</b>
<b>STn Antigen</b> Neu5Ac $\alpha$ 2-6 GalNac - Ser	<b>Tumor cells markers</b> (breast cancer)
<b>Sialyl Lewis X Antigen</b> Neu5Ac $\alpha$ 2-3 Gal $\beta$ 1-4 (Fuc $\alpha$ 1-3) GlcNAc	<b>Cellular Adhesion</b> <b>Fertilisation</b>
<b>Galili Antigen</b> Gal $\alpha$ 1-3 Gal	<b>Hyper accute rejection</b>
<b>Blood Group Antigen : ABO</b> .....	

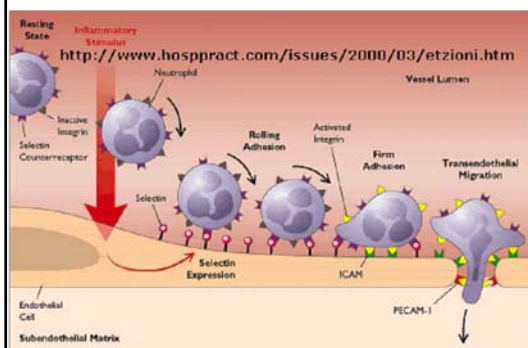
67

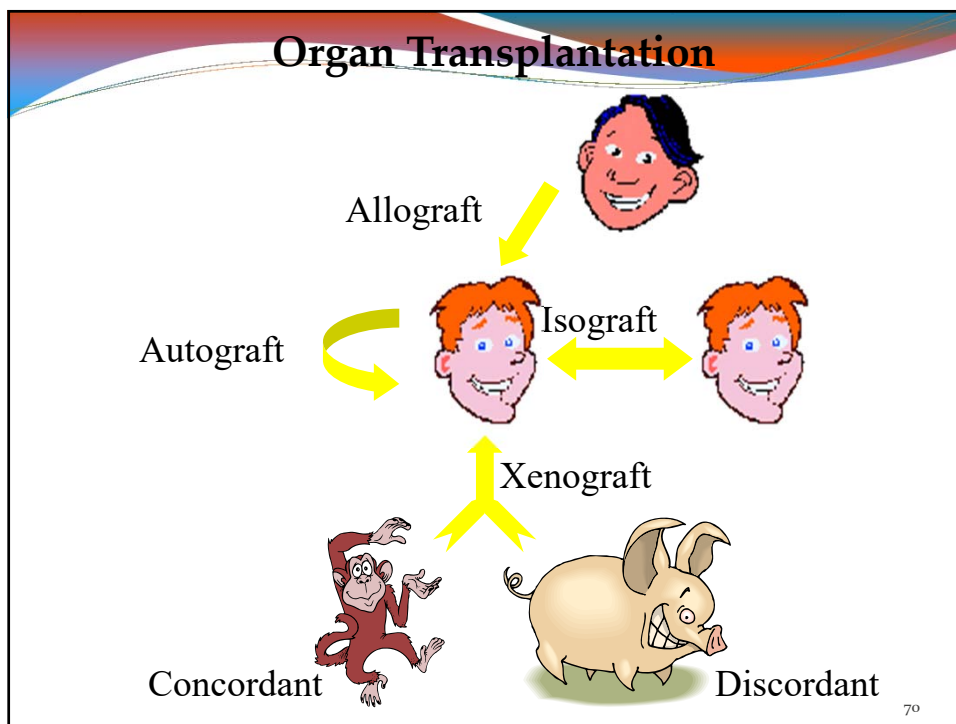
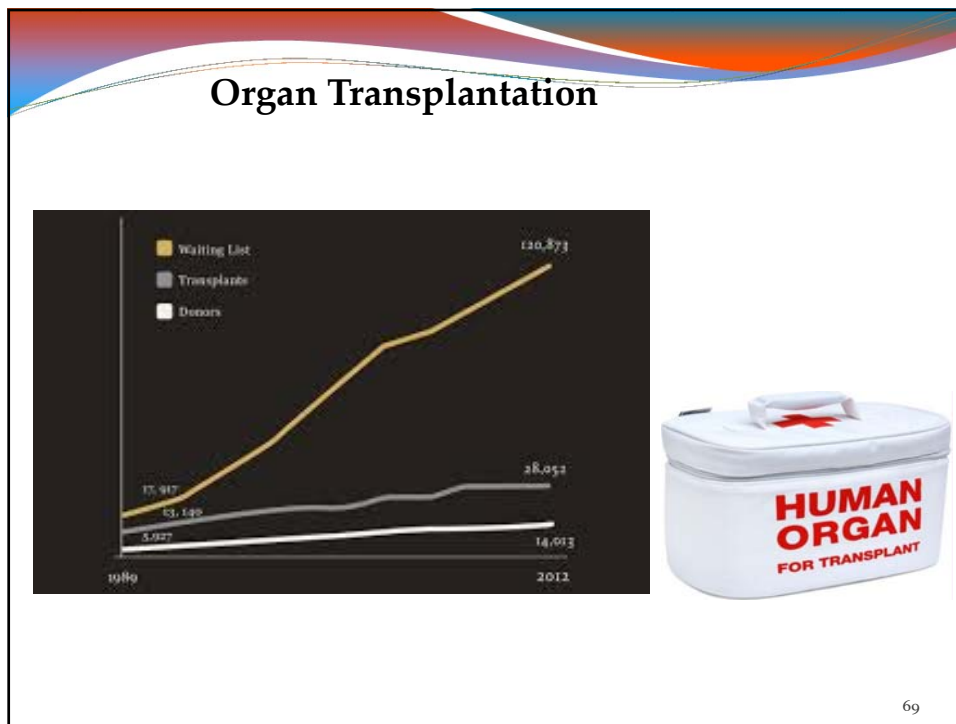
## Cell Cell Interactions : Sialyl Lewis X

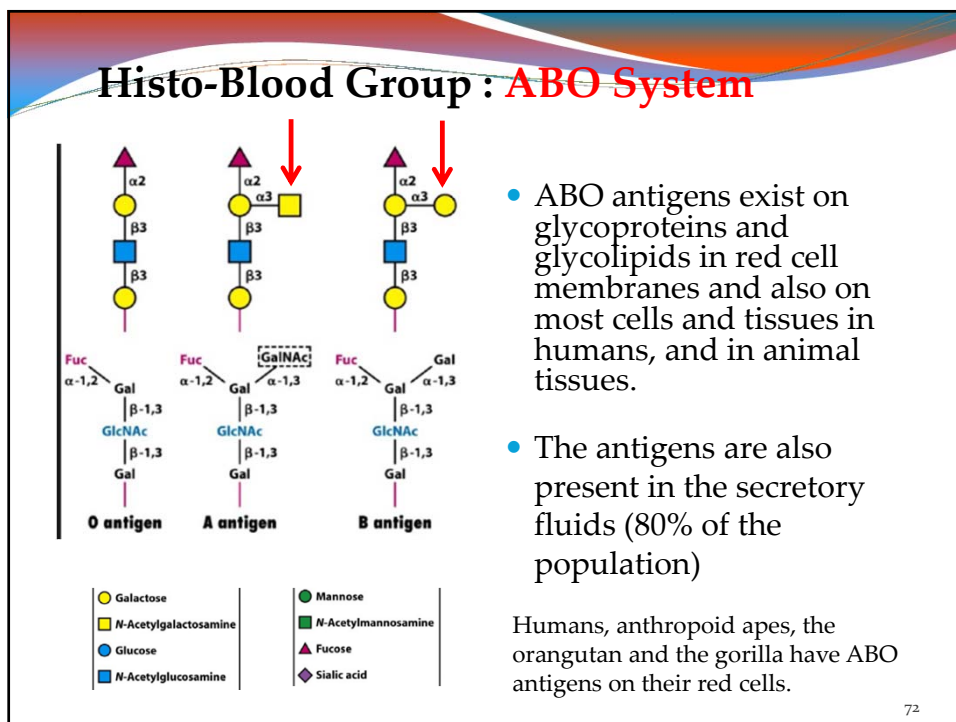
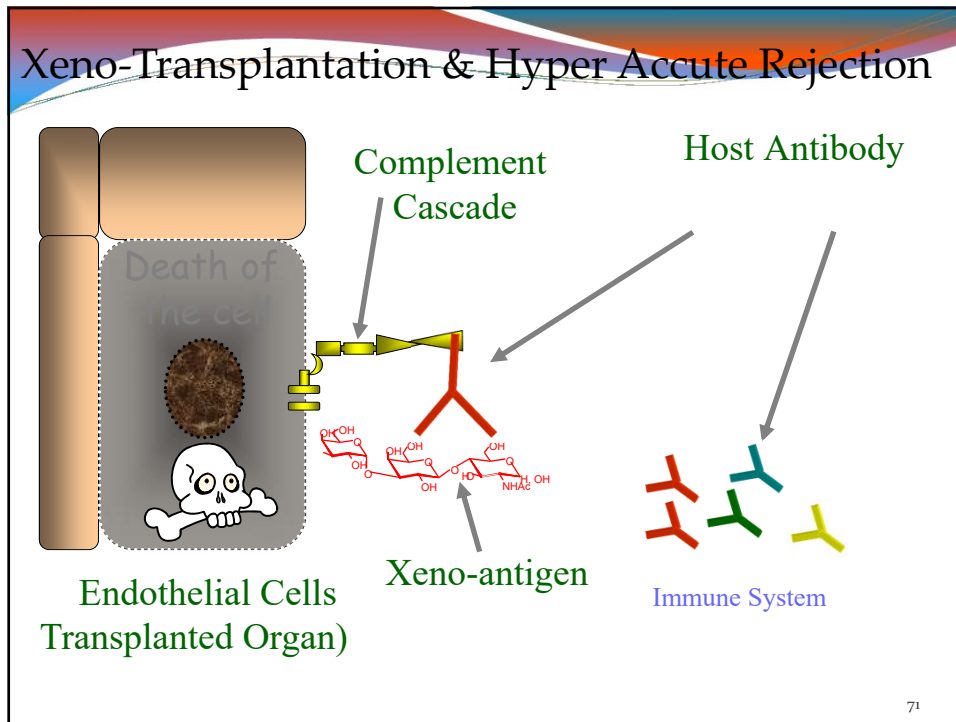
### Fertilisation

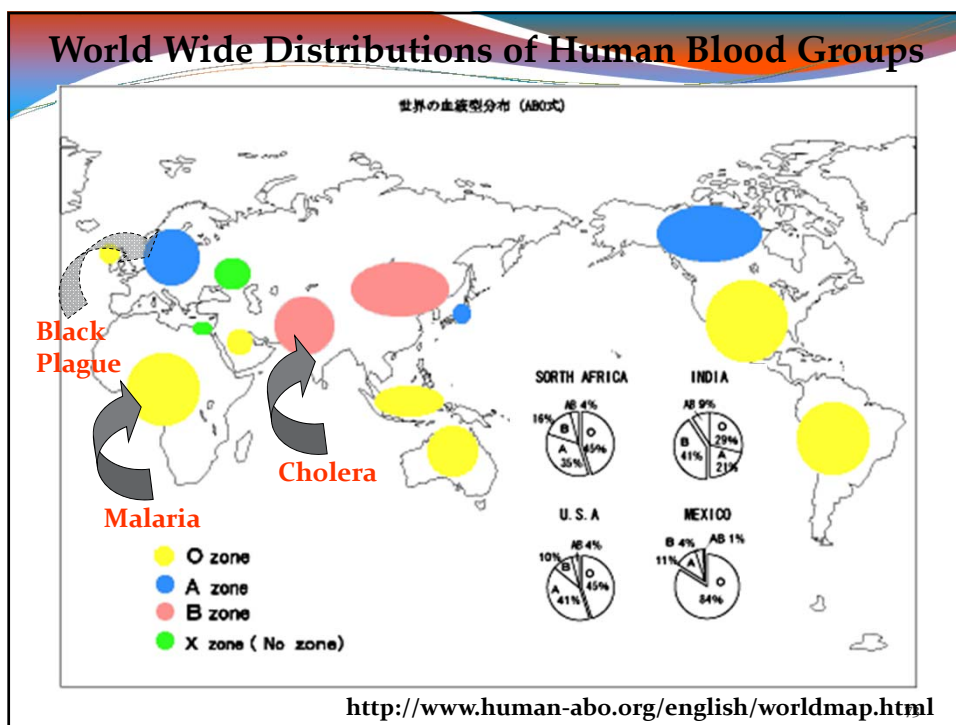
Leucocyte migration & bring macrophage towards the lesion

You would not be here today without sugars!  
Human fertilization is mediated by Sialyl Lewis X











## Our sugars are the result of a co-evolution between animals and micro-organisms

**Biological Role and Significance of Glycan on our Cells?**

**Generate Diversity !!!**


 <http://www.glycopedia.eu/>


news e-chapters **resources** search


 **Sweet Unity Mol : 3D Visualization of Complex...**  
Serge Perez


**Online Databases & Tools**

**A Picture Dictionary of Monosaccharide...**  
Serge Perez

 **Library of Monosaccharide Templates. 1D, 2D,...**  
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 **Library of Bio-active Monosaccharides. 1D,...**  
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 **Workshop Structural Glycoscience. Grenoble...**

 **Glyco Course Firenze 2016**  
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75