



# OTHER BLOOD GROUP SYSTEMS

---

By Mohrah Alalshaikh

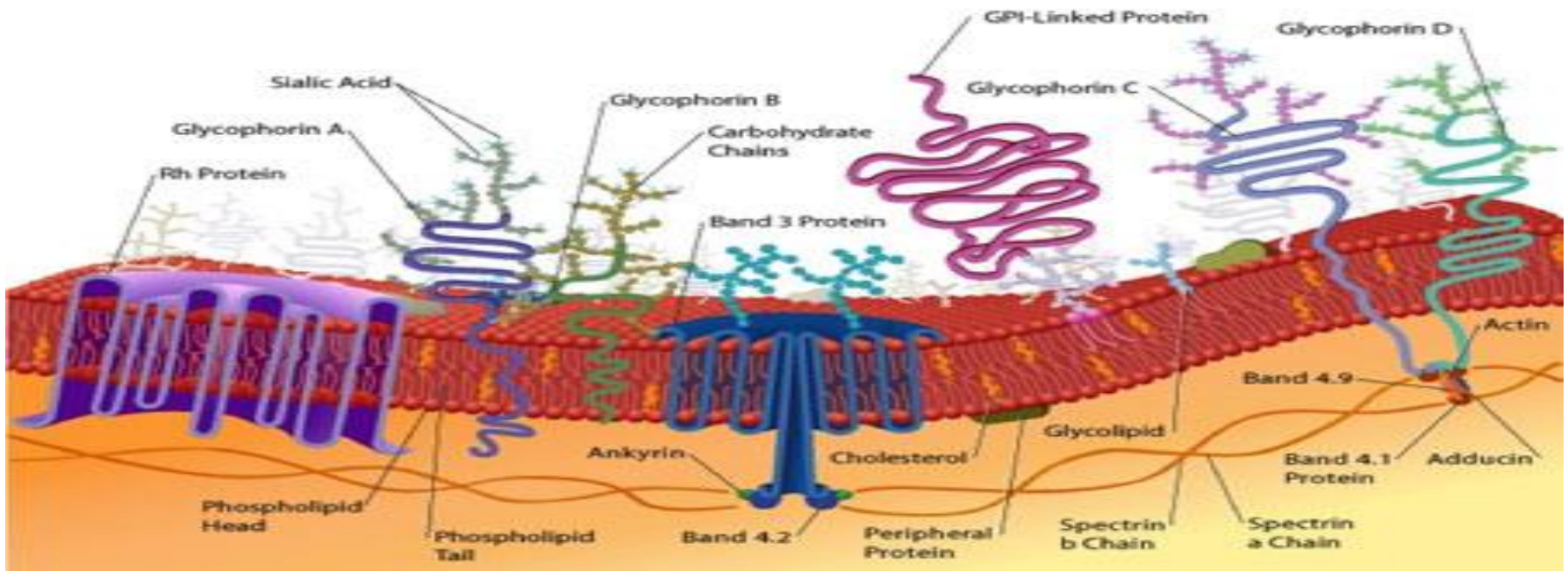
- What are blood group systems you know??
- Why do you think they are important??

# Outline

- What are red blood cell antigens?
- What are blood group systems?
- Types of blood antigens
  - A. Carbohydrate antigens
    - Lewis system
    - P1PK system
    - I system
  - A. Protein antigens
    - MNS
    - Lutheran
    - Kell
    - Duffy
    - Kidd

# What are red blood cell antigens

- Red blood cells (RBCs) bear large number of cell surface structures that can be recognized as antigens by the immune system of individuals who lack that particular structure.



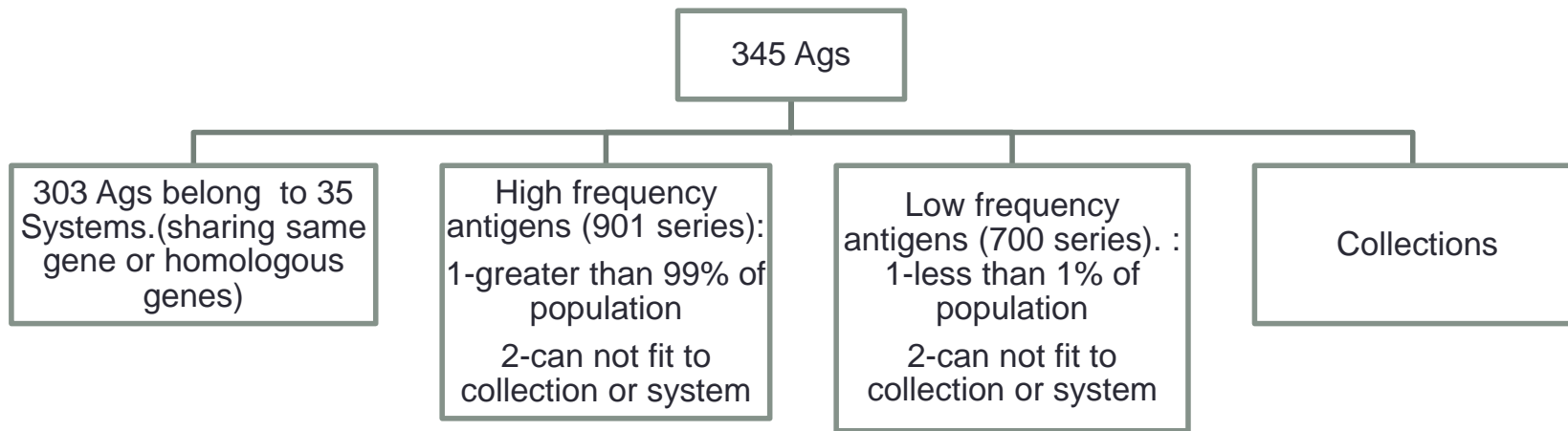
Red blood cell plasma membrane

# Functions of red cell antigens

- These antigens actually have functions. These functions can be classified into six functional groups:
  1. Membrane transporter or channels e.g. Rh, Kidd.
  2. Membrane-bound enzymes e.g. Kell.
  3. Structural proteins e.g. MNS.
  4. Chemokine receptor e.g. Duffy.
  5. Cell adhesion molecule e.g. Lutheran.
  6. Complement regulatory proteins e.g. Cromer.

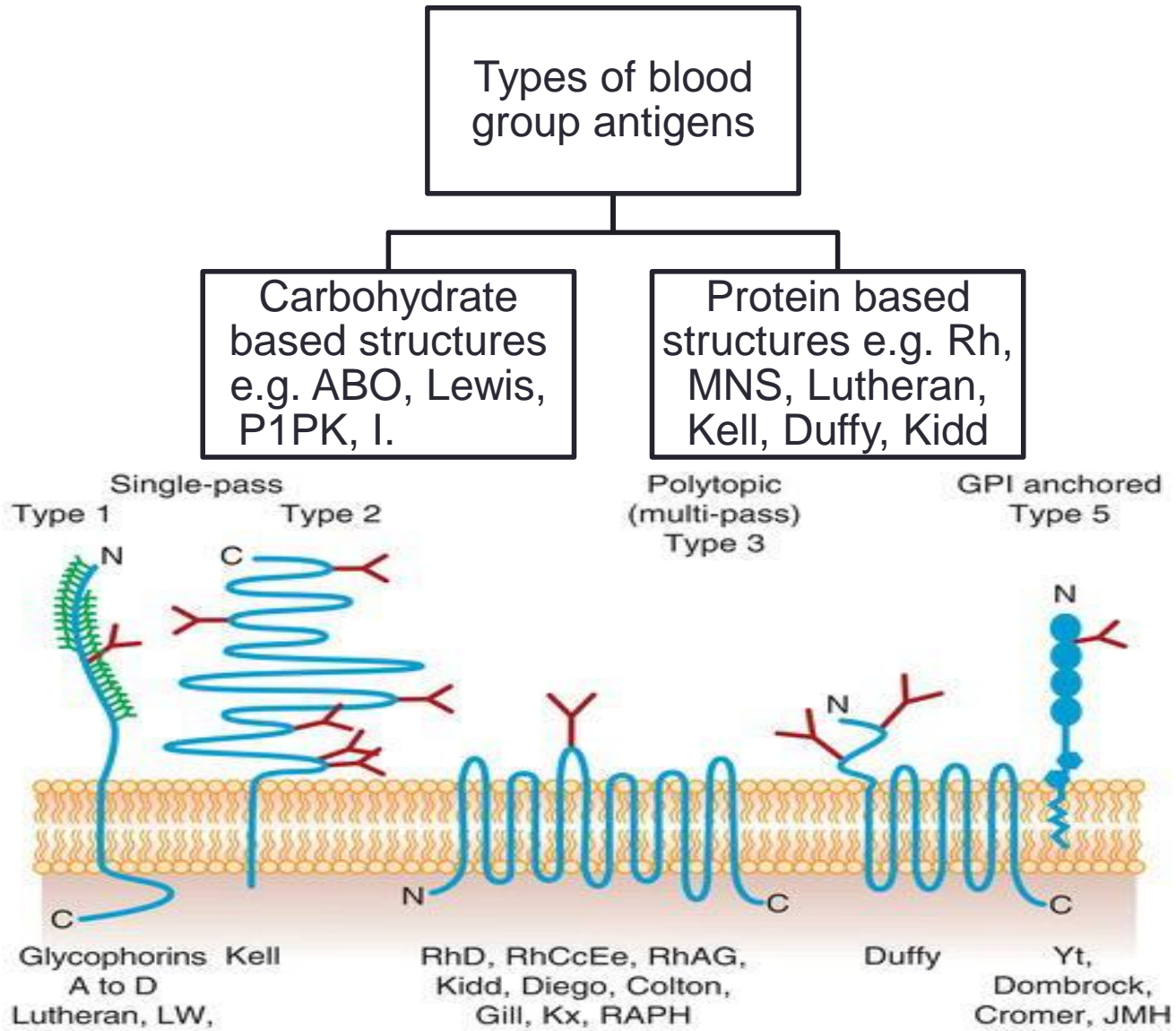
# What are blood group systems

- Currently there are 345 blood group antigens.



- A blood group system consists of one or more antigens, controlled by a single gene (Kell) or by two (Rh) or three (MNS) very closely linked homologous genes.
- Every blood group system has gene (or genes) differ than the other systems.

# Types of blood group antigens

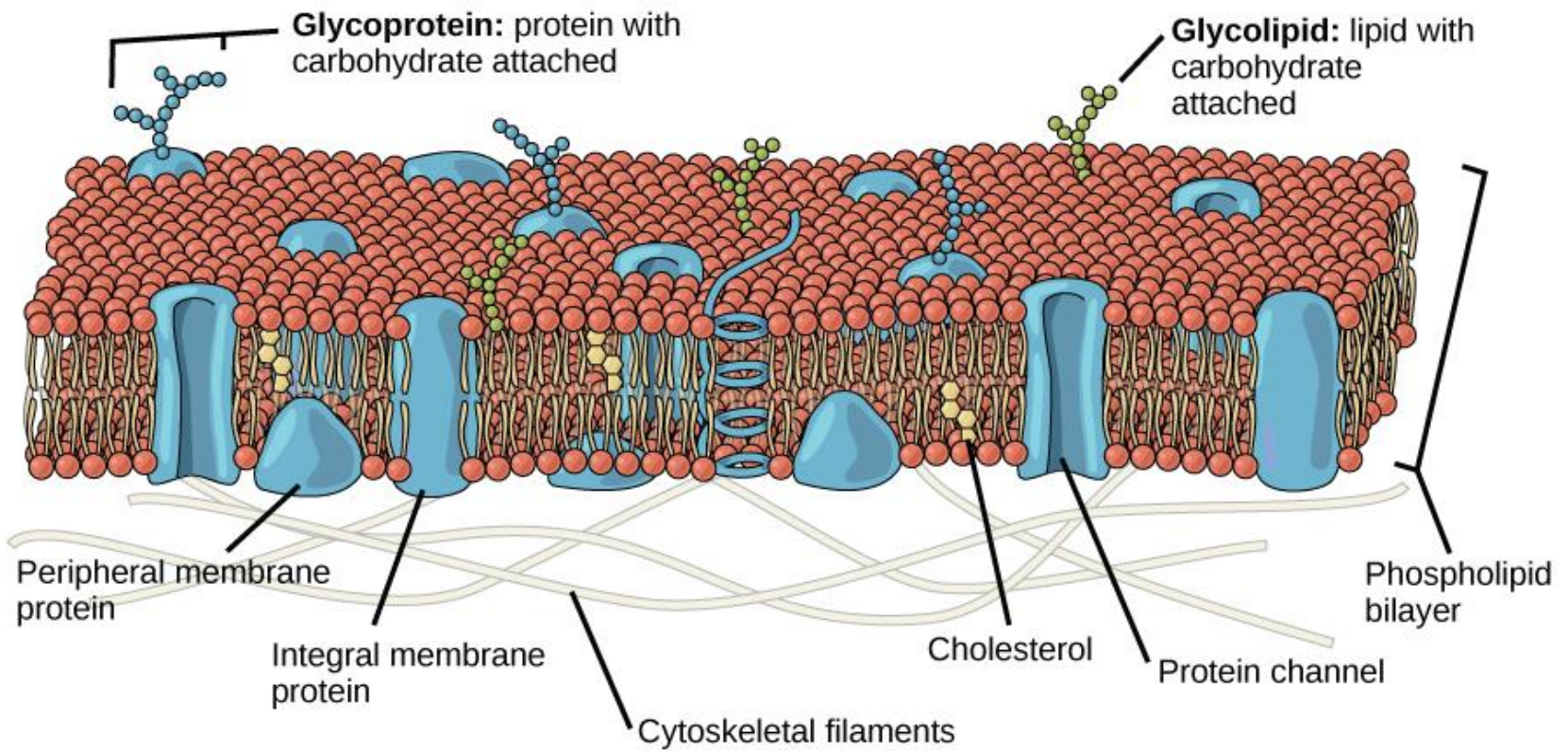


# Carbohydrate antigens

- The carrier is oligosaccharide (3-9 monosaccharides) structures attached to :
  - A- Polypeptides (protein) to form glycoproteins or/and with
  - B- Ceramide (lipid) to form glycosphingolipids.
- Addition of each monosaccharide is done by action of specific glycosyl-transferase enzymes. So, generally transferase enzymes transfer (link) a monosaccharide to an oligosaccharide precursor.



# Glycoprotein and glycolipid



# Lewis system

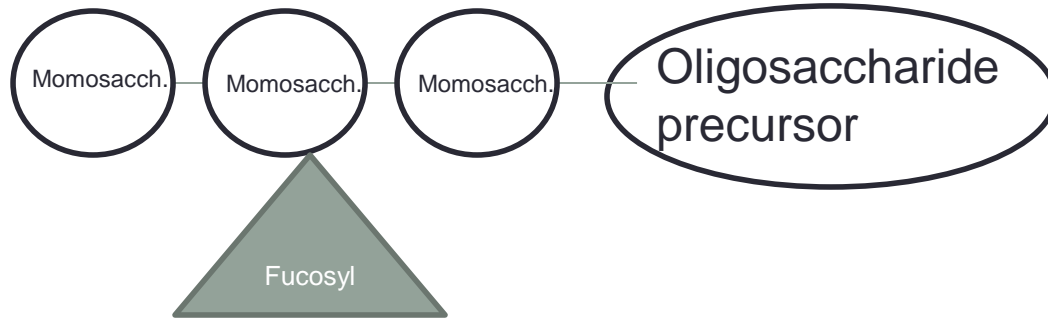
- The two main antigens in the system are Le(a) and Le(b). There are three phenotypes: Le(a+b-), Le(a-b+), and Le(a-b-).
- Lewis antigens are detected red cells and in secretions e.g. saliva, milk.
- The antigens of this system are not synthesized by red cells otherwise they are uptake the antigens from the plasma (the Ag are adsorbed onto the surface of the erythrocyte). The site of synthesis Lewis antigens is still unknown.



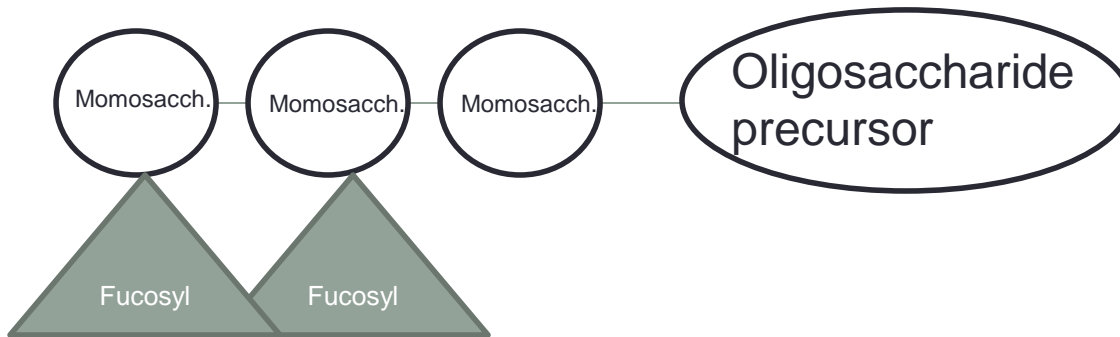
# Lewis antigens

- Lewis antigens are not well developed in newborns. Generally newborn are Le(a-b-). Also they may be detected as Le(a+b+) before becoming Le(a+b-).
- *Le* (*FUT3*) gene encodes the system antigens. It can be *LeLe* or *Lele* or *lele*. *le* is not functional, recessive allele, so people with *lele* genotype are Le(a-b-).
- There is relation and interaction between *Le* and *Se* (the secretor gene) genes. The individual *Se* and *Le* genotype determines the Lewis phenotype. In the present of *Se* gene the phenotype will be Le(a-b+), BUT in individual who has silent *Se* (inactive gene, *sese*) the phenotype will be (a+b-)

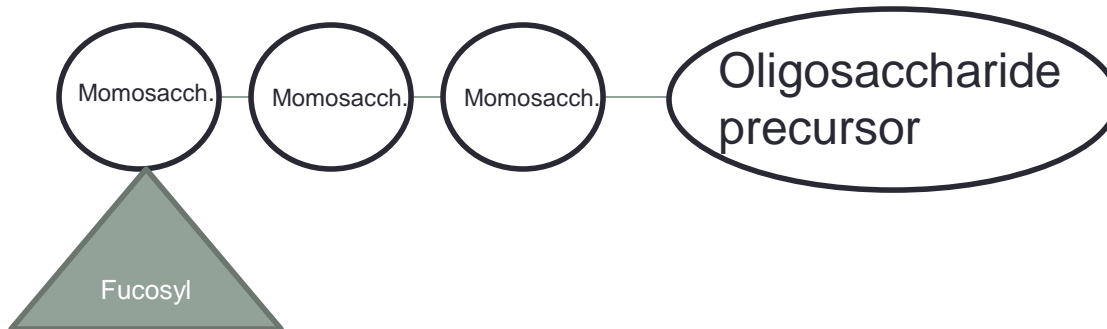
# Lewis Ag structures



Le(a) molecule  
Le gene but NO Se gene.  
Le gene responsible for linking fucosyl (monosaccharide) to the subterminal monosaccharide.



Le(b) molecule  
Le gene + Se gene



H molecule  
Se gene responsible for linking fucosyl (monosaccharide) to the terminal monosaccharide

# Le and Se genes

- The relation between Le and Se genes:

| Genotype                     |                              | Antigens in secretions |                 |
|------------------------------|------------------------------|------------------------|-----------------|
| Lewis                        | Secretor                     | Le <sup>a</sup>        | Le <sup>b</sup> |
| <i>Le/Le</i> or <i>Le/le</i> | <i>Se/Se</i> or <i>Se/se</i> | +                      | +               |
| <i>Le/Le</i> or <i>Le/le</i> | <i>se/se</i>                 | +                      | -               |
| <i>le/le</i>                 | Any                          | -                      | -               |

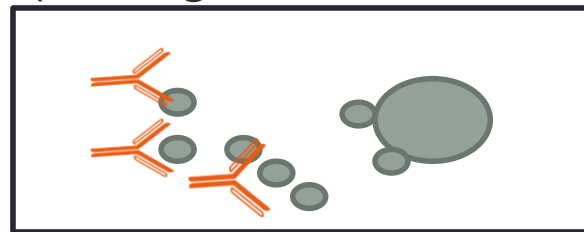
(Adapted from Daniels, Geoff, 2013, [Human Blood Groups](#))

# Lewis antibodies

- Le Antibodies (Abs) are usually 'naturally occurring' antibodies. Naturally occurring means that the person has the Abs without be exposed to the Ags previously such as in transfusion or pregnancy.
- They are mainly from IgM class but there are some of IgG class.

## Clinical significant of Lewis Ab:

- Although Lewis Abs are common, they usually do not cause hemolytic transfusion reactions (HTR). Most probably because most Lewis Abs are IgM so they not react at 37c.
- Also they do not cause hemolytic disease of newborn (HDN) because the mothers Abs are neutralized (become ineffective) by the fetuses Ags present in the secretion (the Ags not adsorbed yet onto the fetuses red cells).



# P1PK system

- As with any carbohydrate Ags, the sugars which express the different Ags of the P1PK system are attached to a precursor oligosaccharide by the action of a transferase enzyme.
- These oligosaccharide precursors are attached to the red cell membrane via ceramide (lipid).
- The system currently includes three Ags: P1, Pk, and NOR. (Hellberg A, 2013, immunohematology).
- The Ags are controlled by *A4GALT* gene.

# P1PK system

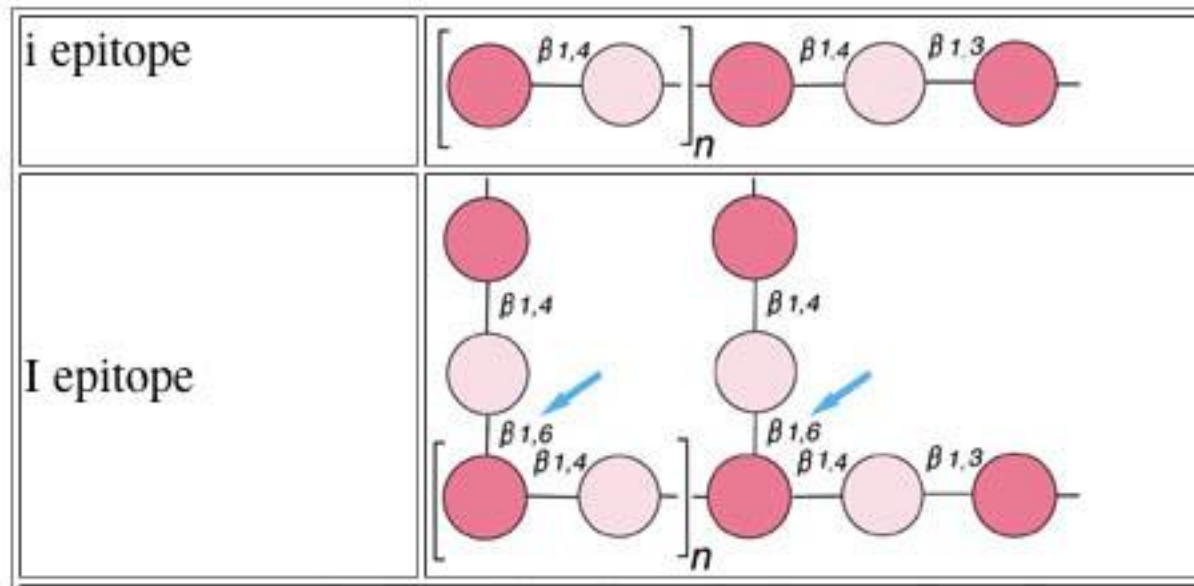
- Different combinations or absences of 2 antigens, P1 and P(k), forming 5 different P1PK blood group system phenotypes: P1, P2, P1k, P2k, and p.
- The P1 red cell phenotype is the most common phenotype with a prevalence of approximately 75%. The P2 red cell phenotype is defined and has a prevalence of about 25%.
- P1Pk Ags are widely distributed on the body.
- P1PK Abs are naturally occurring Abs and mainly of IgM class. Generally they are weak and cold-reactive antibody, so they do not normally involve in HTR or HDN.



# I system

- There is one Ag in this system: I . It is a carbohydrate based structure carried on glycolipid or glycoproteins.
- The gene encoded the relevant transferase enzyme is *GCNT2*. This enzyme transfer i Ag, which is belong to Ii collection, to I Ag.
- I is expressed by branched structures while I by linear structure.
- Newborns red cells express the i Ag. With time i Ag converted to I Ag. Most adult red cells express large amount of I Ag and very little of i Ag. Rarely adult cells continue to express i Ag. Most probably due to inactivated mutation in the branching enzyme (*GCNT2*).
- The I and i Ags are widely distributed and they are expressed on other cells e.g. lymphocytes and platelets. Also found on fluids e.g. saliva and milk.

# I and i Ags structures



([http://www.ncbi.nlm.nih.gov/projects/gv/rbc/xslcgi.fcgi?cmd=bgmut/systems\\_info&system=i](http://www.ncbi.nlm.nih.gov/projects/gv/rbc/xslcgi.fcgi?cmd=bgmut/systems_info&system=i))

# I and i Abs

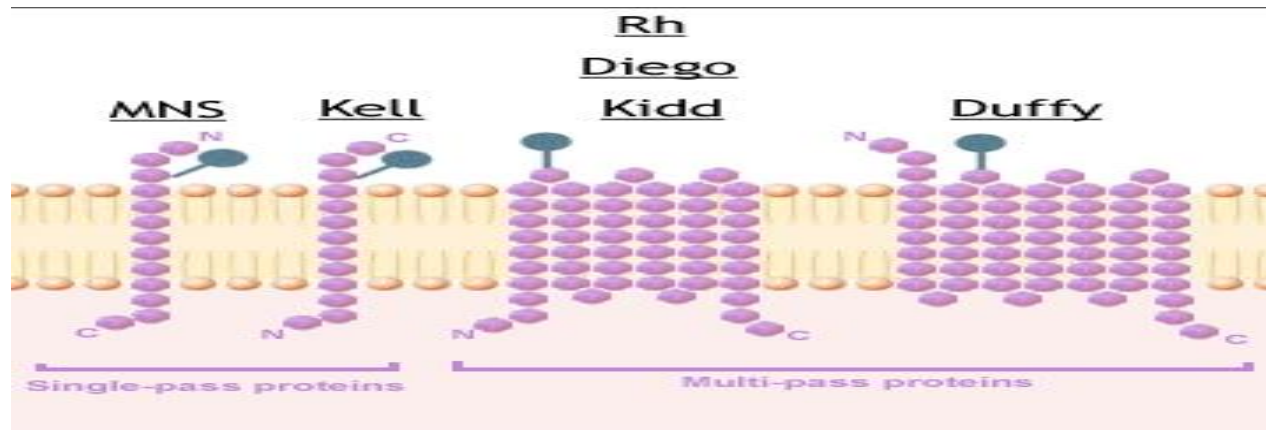
- They are naturally Ab of IgM class.
- They are auto-Abs and they the most common autoantibody found in cold hemagglutinin disease.
- Anti-I does not cause hemolytic disease of newborn, while anti-i can cause. WHY??

# Protein antigens

- In protein based systems, the gene directly control the Ags. Mutations in the gene may cause changes in the encoded amino acid leading to have different blood group. For example:

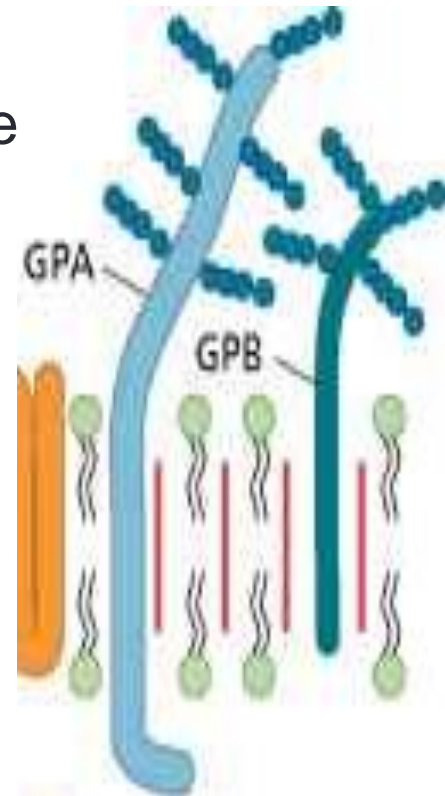
|              |                    |                    |
|--------------|--------------------|--------------------|
| For example: | <b>G</b> GU CAA    | <b>G</b> AU CAA    |
|              | Gly at position 42 | Asp at position 42 |
|              | Fy(a)              | Fy(b)              |

- By contrast, in carbohydrate systems, the genes encode transferase enzymes that responsible for synthesizing the Ags.



# MNS system

- There are 43 antigens in this system. M, N, S and s Ags will be studied. MNS Ags are produced by three genes: *GYPA*, *GYPB* and *GYPE*. These genes are present at very closely loci.
- The M and N Ags are expressed on glycoporphin A. The S and s Ags are expressed on glycoporphin B.
- The Ags are differ due to a different amino acid sequence on the glycophores. Glycophorens are proteins on the red cell membrane. These proteins play a role in the negative charge of the red cells.
- The MNS Ags are well developed at birth.

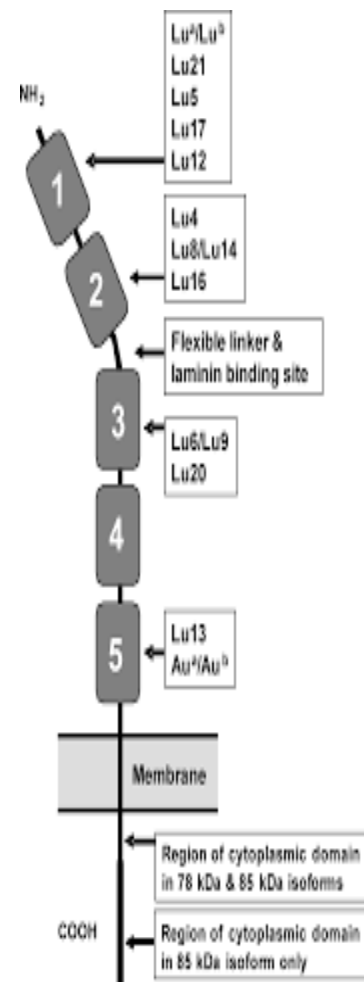


# MNS Abs

- Anti-M and anti-N are naturally occurring Abs. They are from IgM and IgG classes. They may cause HTR and rarely cause mild HDN.
- Anti-S and anti-s are immunogenic. This means that the body have to be exposed to the Ag to activate the immune system to produce the 'immunogenic Abs'. They are mainly of IgG class. They may cause HTR and mild to sever HDN.

# Lutheran system

- There are 19 Ags in this system. We will consider Lu(a) and Lu(b) Ags. The Ags are expressed on Lutheran glycoprotein molecule.
- Lu Ags are poorly developed at birth and poorly immunogenic.
- Ags of this system are encoded by *Lu* gene.
- The difference between Lu(a) and Lu(b) is a single nucleotide change: Guanine (G) to Adenine (A) transition in the gene.
- More than 90% of tested population are Lu(a-b+)



# Lutheran Abs

- Anti-Lu(a) is naturally occurring or immunogenic. It is usually from IgM class.
- Anti-Lu(b) is always immunogenic (usually produces after transfusion or pregnancy).
- Both anti-Lu(a) and anti-Lu(b) rarely cause mild HTR.
- Also they have not cause HDN. This is may be because Lu Ags are not develop well at birth.



# Kell system

- There 35 Ags in this system. We will study K and k Ags. Kell Ags are encoded by *KEL* gene and they expressed on Kell glycoprotein.
- More that 80% of the studied populations have (K-k+) phenotype.
- There are rare recessive silent *KEL* gene which produce NO Kell Ags. So, individual with Kell-null genotype all the 35 Kell Ags are absent from their red cell membrane.
- K Ag is the most immunogenic antigen outside the ABO and Rh systems.
- Kell Ags are well developed at birth.

# Kell Abs

- They are immunogenic Abs and generally from IgG class. All Kell Ags are considered as clinically significant Abs.
- Anti-K is the most common immunogenic Abs outside ABO and Rh systems. It can cause severe HTR also sever HDN. Anti-K from the mother can destroy infants immature erythrocytes result in sever anemia.
- Anti-k also can cause sever HTR and HDN.
- It is very important to note that the present of foreign Ags does NOT usually stimulate the immune system to produce Abs. For example, not all Lu(a+b-) people produce anti-Lu(b) when they received Lu(a+b+) blood.

# Duffy system

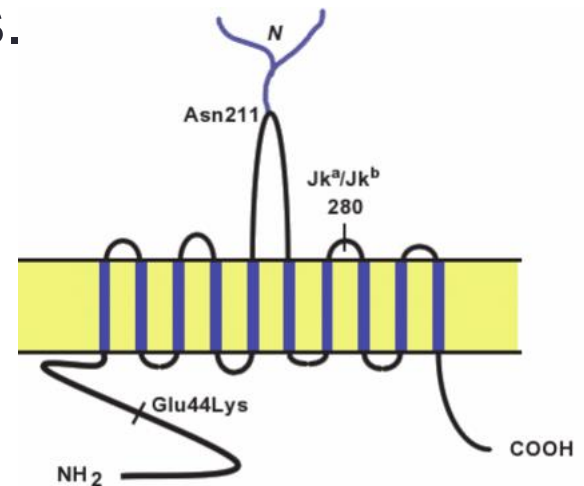
- There are six Ags in this system. They are encoded by *Fy* (or *DARC*) gene. We will study Fy(a) and Fy(b).
- Duffy Ags are expressed on Fy glycoprotein. This glycoprotein is a chemokines receptor.
- Fy(a-b-) individual who inherited two copies of Duffy silent gene lack the Fy glycoprotein. This condition is common in Black people (68%) but very rare in White people. This is interesting because Fy glycoprotein is the attachment site of Malaria parasite. So the absence of Duffy glycoprotein from red cells plays a role in protecting the individual from Malaria because the parasites cannot attach to the cell membrane to enter the cell.
- Duffy Ags are well developed at birth. Also they are moderately immunogenic.

# Duffy Abs

- They are immunogenic Abs and from IgG class. Some people with Duffy Abs where stimulated during pregnancy but MOST of them due to transfusion.
- Anti-Fy(a) and anti-Fy(b) can cause mild to sever HTR and HDN.

# Kidd system

- There only three Ags in this system. Jk(a) and Jk(b) will be studied.
- Kidd Ags are encoded by *Jk* gene and they are expressed on Kidd glycoprotein.
- The function of Kidd glycoprotein is urea transporter.
- The Ags are well developed in newborns.



# Kidd Abs

- They are immunogenic Abs and from IgG class.
- They can cause severe HTR. They can cause mild HDN.
- Some times, it is hard to detect Kidd Abs because the antibody levels in patients often fall very quickly. So, donor blood may appear as compatible then the patient (recipient) suffer from HTR!

# Summary

- Blood antigens have their own functions in addition to their roles in transfusion.
- Different Ags become in a one system because they are controlled by one gene or by two or three closely linked genes.

- There are two type of Ags :

A-Carbohydrate Ags controlled indirectly by genes encode transferase enzymes.

B-Protein Ags controlled directly by their genes.

- The nature of different blood systems (3 sugar and 5 protein systems) , number of Ags in each system and most important Ags, the controlled gene, there development in newborns and the clinical significant of their Abs.