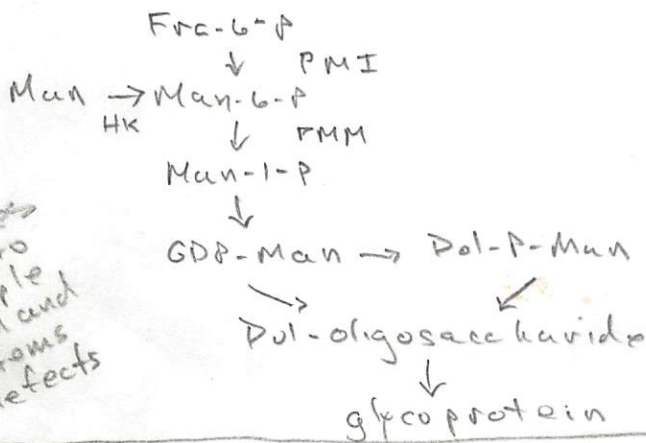


- Much of what we know about glycan function derives from studies of mutant cell lines, mice and other model organisms, and naturally occurring diseases
- Congenital Disorders of Glycosylation (CDG)
 - typically diagnosed by abnormal isoelectric focusing of serum transferrin / mass spectrometry

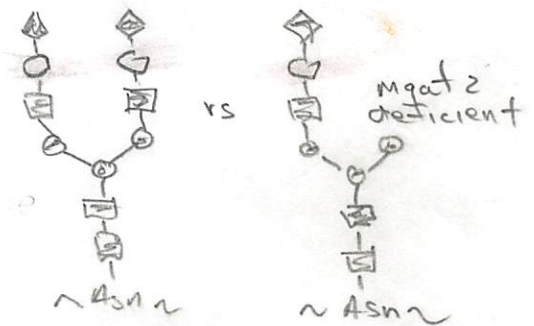
(i) Underglycosylation due to reduction in precursor dolichol-P-glycan



Diseases lead to multiple organ and systems defects

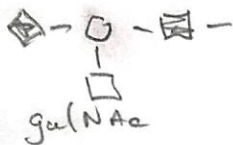
c	CDG-I	CDG-II	
			Sia ₄
			Sia ₃
			Sia ₂
			Sia ₁
			Sia ₀

(ii) Reduction in size or complexity



• Gain of function Mutations

- misexpression of a glycosyltransferase
- eg. GalNAcT misexpression in endothelial cells results in

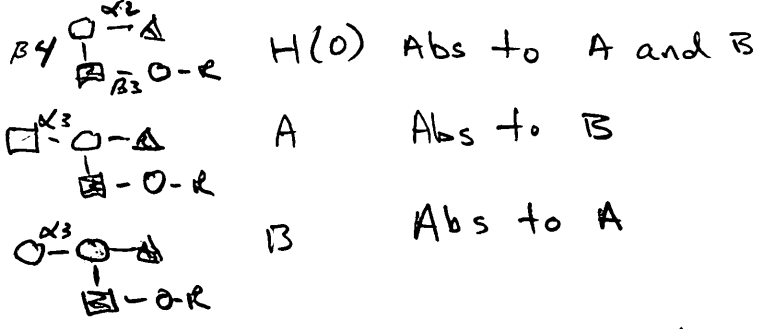


→ clearance of glycoprotein by AMR in the liver. This was detected as a bleeding disorder due to deficiency of von Willebrand factor

eg. Addition of a glycosylation site in a glycoprotein
 Immunodeficiency caused by T168N mutation in Interferon gamma R2 chain of IFN-γ receptor - no longer binds to IFN-γ

Transplantation

- Transfusion requires matching of ABO blood groups



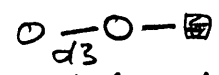
Where do these antibodies arise?
i.e. what's the antigen?

Match RBC (donor) to recipient

A → A or AB, B → B or AB, O → A, B, O, AB

- Organ transplantation

Animals express α Gal epitopes but humans do not; humans have high titer Abs to α -gal, which prevents organ xenotransplantation



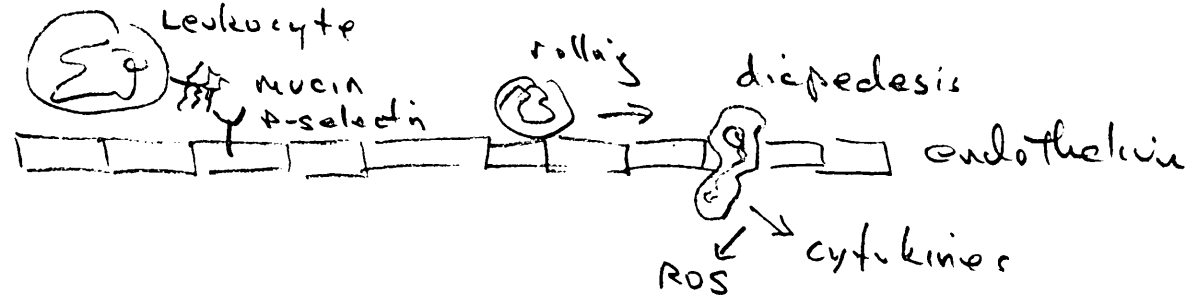
- Meat allergy

overload of IgE antibodies to α -Gal lone star tick - idea is that tick carries α gal due to blood meal from animal. Bite induces immune system to respond with IgE, then eating meat induces allergic reaction - "Beano?"

"Beano?"

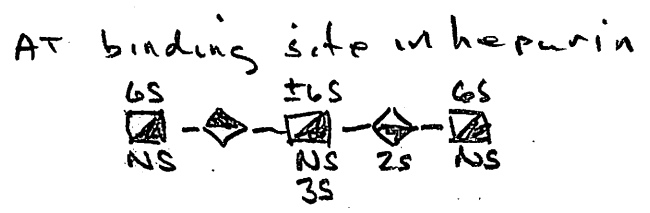
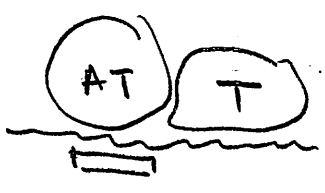
• Reperfusion Injury

- Stroke, myocardial infarct, hypovolemic shock induces P-selectin expression on activated endothelium.
- Leukocytes roll, extravasate, and cause subsequent tissue damage



Heparin

- Porcine intestinal heparin is a powerful anticoagulant
- Works by binding to and activating antithrombin which then inhibits Factor IIa (Thrombin) and Factor Xa (FXa)



- Thrombin inhibition requires dpts containing the pentasaccharide and a flanking sulfated sequence to bind thrombin
- FXa inhibition only requires the pentasaccharide so LMWH (derived from heparin by limited degradation) or synthetic penta (Arixtra) is adequate - long half life in circulation
- Heparin also binds to many other proteins

PF4 - heparin complexes can induce antibodies which result in reaction with and activation of platelets via FcγIIa receptors on platelet → clots and ↓ platelets (thrombocytopenia)

platelet factor 4

HIT

- Acquired anticoagulation

Cirrhosis or hepatocarcinoma results in shedding of anticoagulant heparan sulfate into circulation

Cancer

Tumor cells express oncofetal antigens (glycans) on glycoproteins and GSLs

Microevolution based on survival / rapid proliferation of tumor cells

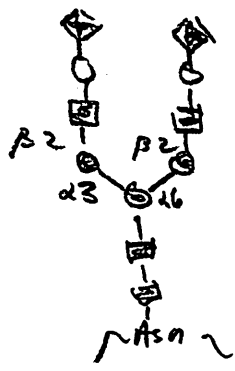
- Do changes explain traits of tumor cells and disease symptoms?

1. Changes in GAG composition

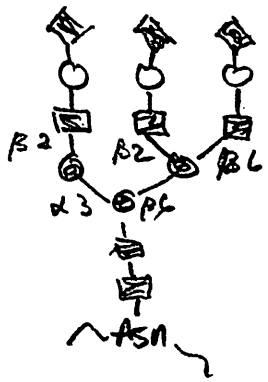
- HA ↑ in many tumors - increases tissue volume and modulates signaling and survival
- HS changes in composition - altered growth factor activation eg. wnts
- CS ↑, increases cell mobility

2. Changes in sialylation

- mgat5 activation



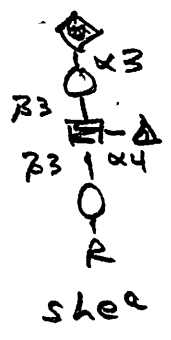
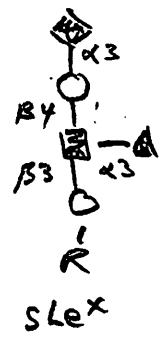
Mgat5
GNTV



causes increase in metastasis by unknown mechanism - genetic data in mice is compelling
Mention mgat 5

3. Altered Adhesion

- many tumors express sLex and sLea



sLex binds to P-selectin so tumor cells expressing sLex can bind to platelets and endothelial cells

Show slide 1

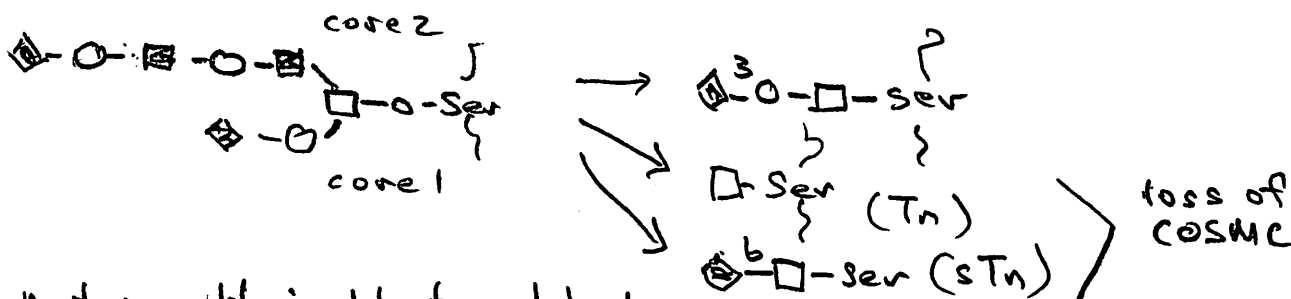
- Tumor cells mimic leukocytes, adhere and invade
- Many tumors overexpress mucins, which can facilitate platelet cloaking and adhesion to endothelial cells
- shed mucins can induce crosslinking of platelets and formation of thromboemboli (part of Trousseau Syndrome - coagulopathy associated with cancer)

Glycan Biomarkers and Therapy for Cancer

- can monitor therapy using antibodies to diagnostic markers
- develop immunotherapy based on antibodies to biomarkers
- eg. GD2 in melanoma and neuroblastoma

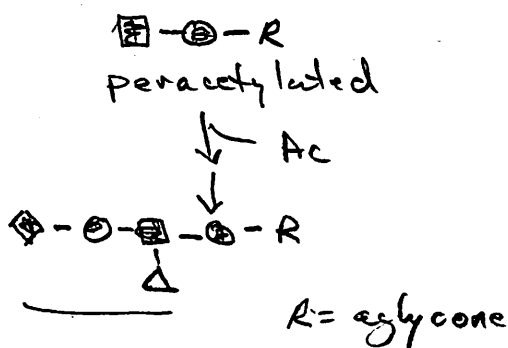
CA19-9 (sLe^a) - colon, pancreatic tumors, present as shed mucin in plasma
 CA125 (Muc16) - ovarian tumor

Mucins



• Net result is that antibodies can be generated to Muc core

Inhibitors of sLe^x formation decrease metastasis



- decoys assembly of sLe^x on mucins and glycoproteins
- blocks experimental and spontaneous metastasis by blocking adhesion

Many other changes in glycans occur in cancer that modulate immune response or that can increase inflammation