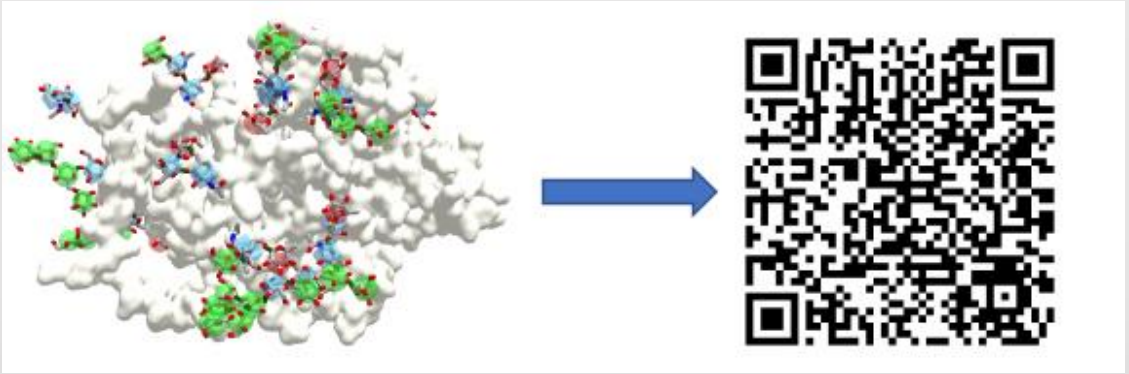
The Sugar Code and its Readers



A code is defined by the nature of the symbols, which are used to generate information-storing combinations. Like nucleic acids and proteins, polysaccharides are ubiquitous, and they are a biochemical platform for establishing molecular messages.

Avraham Raz Ph.D.

Paul Zuckerman professor of Oncology and Pathology

Amino acids and Nucleotide bases constitute the first and the second alphabets of life.

Monosaccharides(Simple Sugars) are the third alphabet of life;

The letters of the sugar code system excel in coding capacity by making an unsurpassed versatility for isomer formation possible by variability in anomery and linkage position of the glycosidic bond, ring size, and branching.

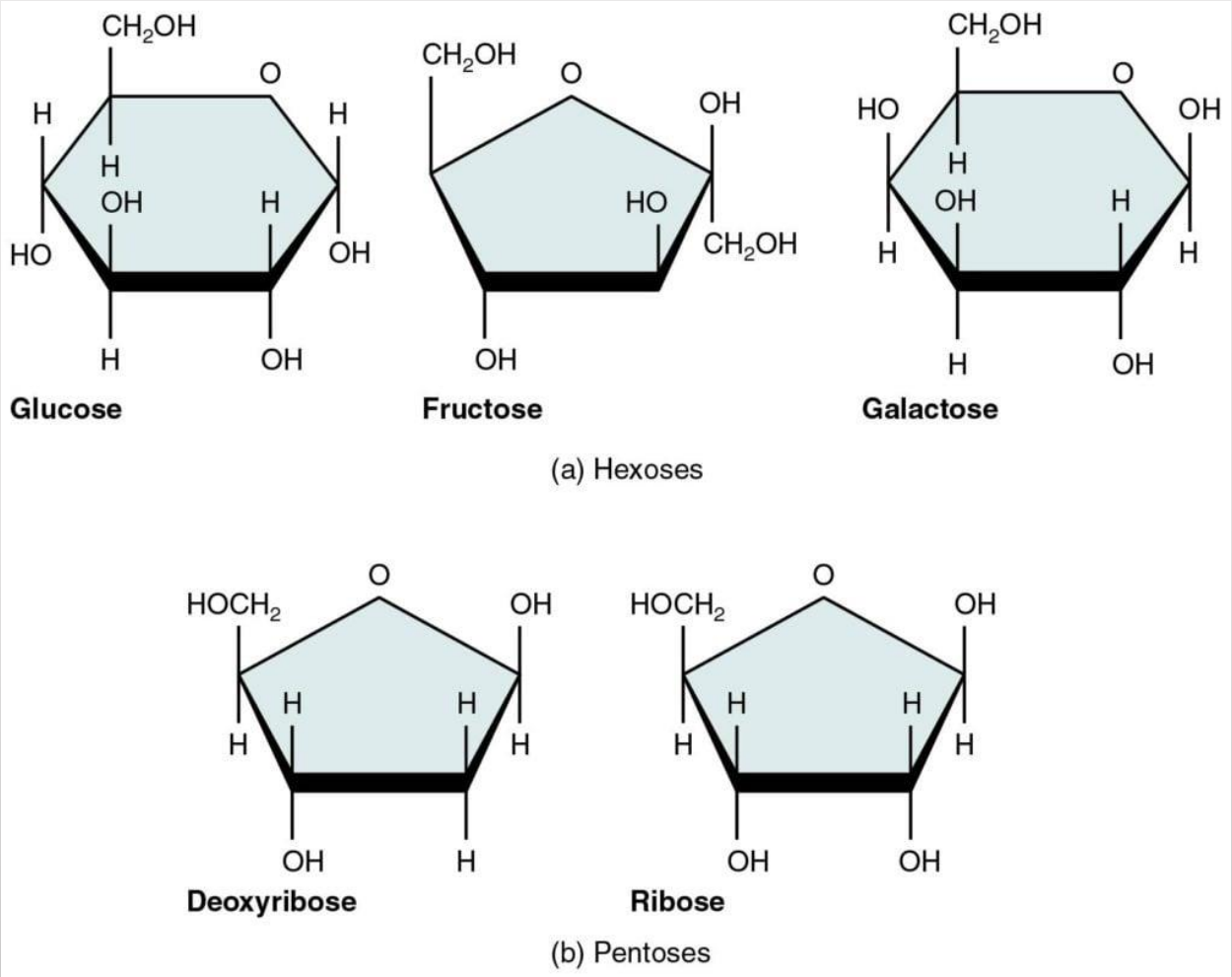
Sugars = Carbohydrate

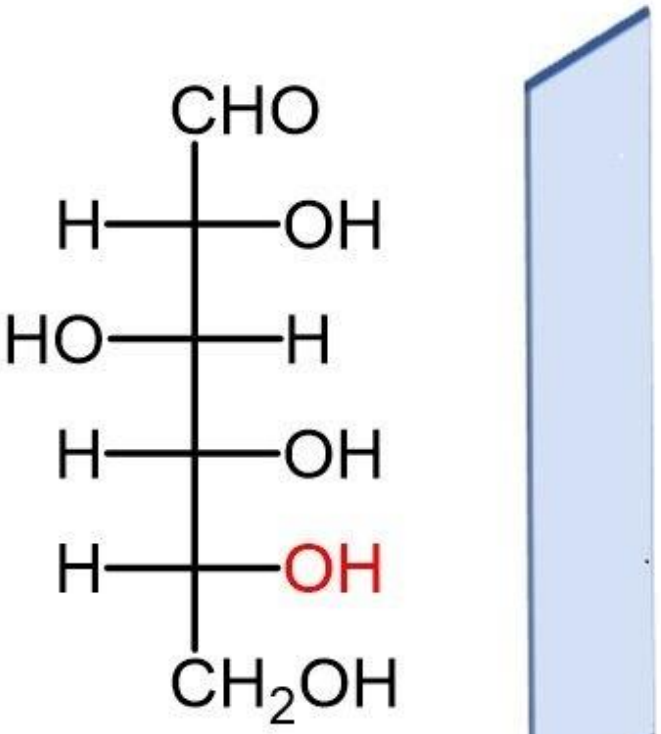
Carbohydrates are biological molecules made in a ratio of roughly one carbon atom (C) to one water molecule (H_2 O). This composition gives carbohydrates their name: they are made up of carbon (carbo-) plus water (-hydrate).

Carbohydrate Readers –LECTINS

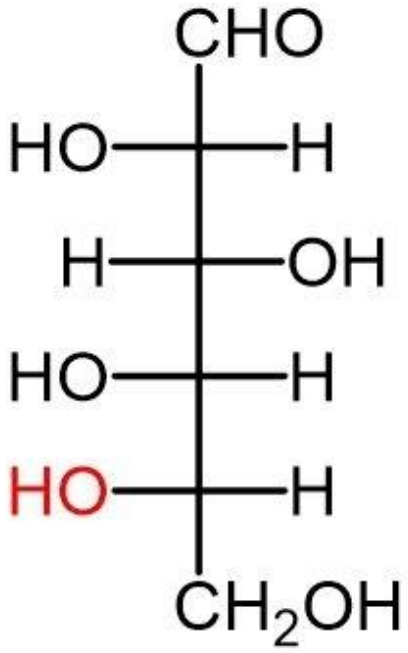
Lectins (proteins that bind to carbohydrates) ‘read’ the glycan-encoded information.

Monosaccharides





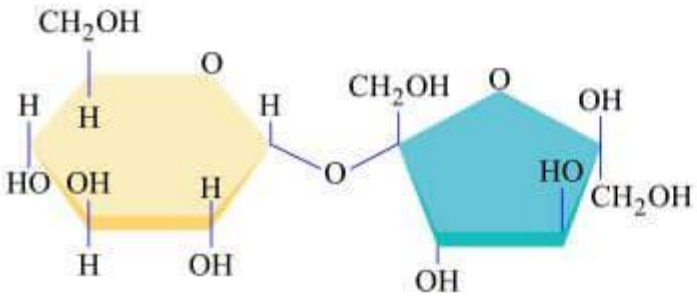
D-glucose



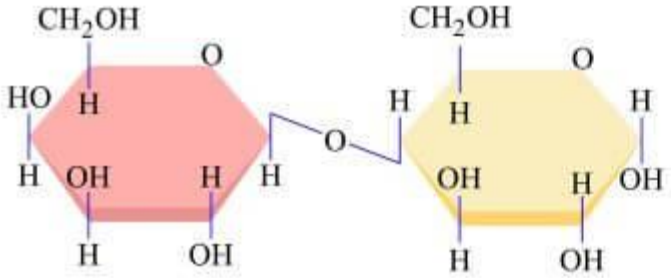
L-glucose

Enantiomers

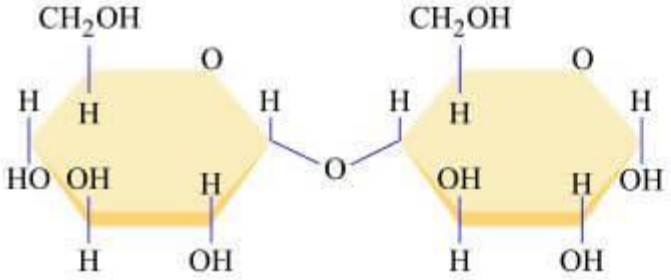
Disaccharide



Sucrose
Glucose and Fructose

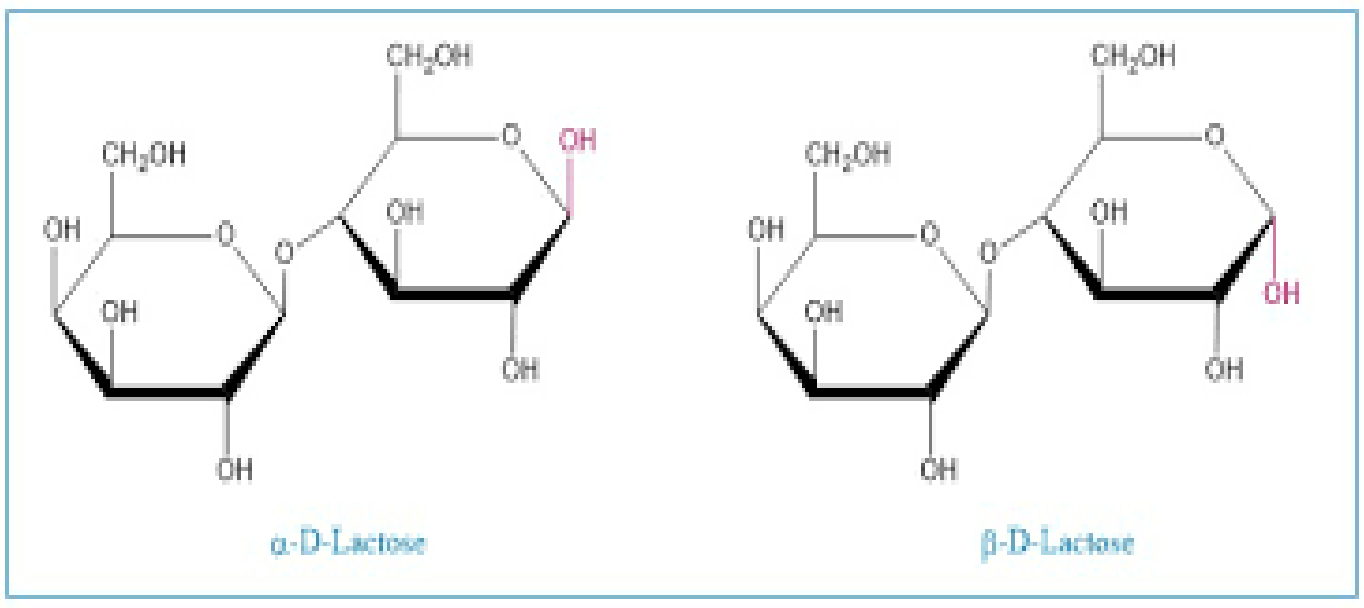


Lactose
Galactose and Glucose



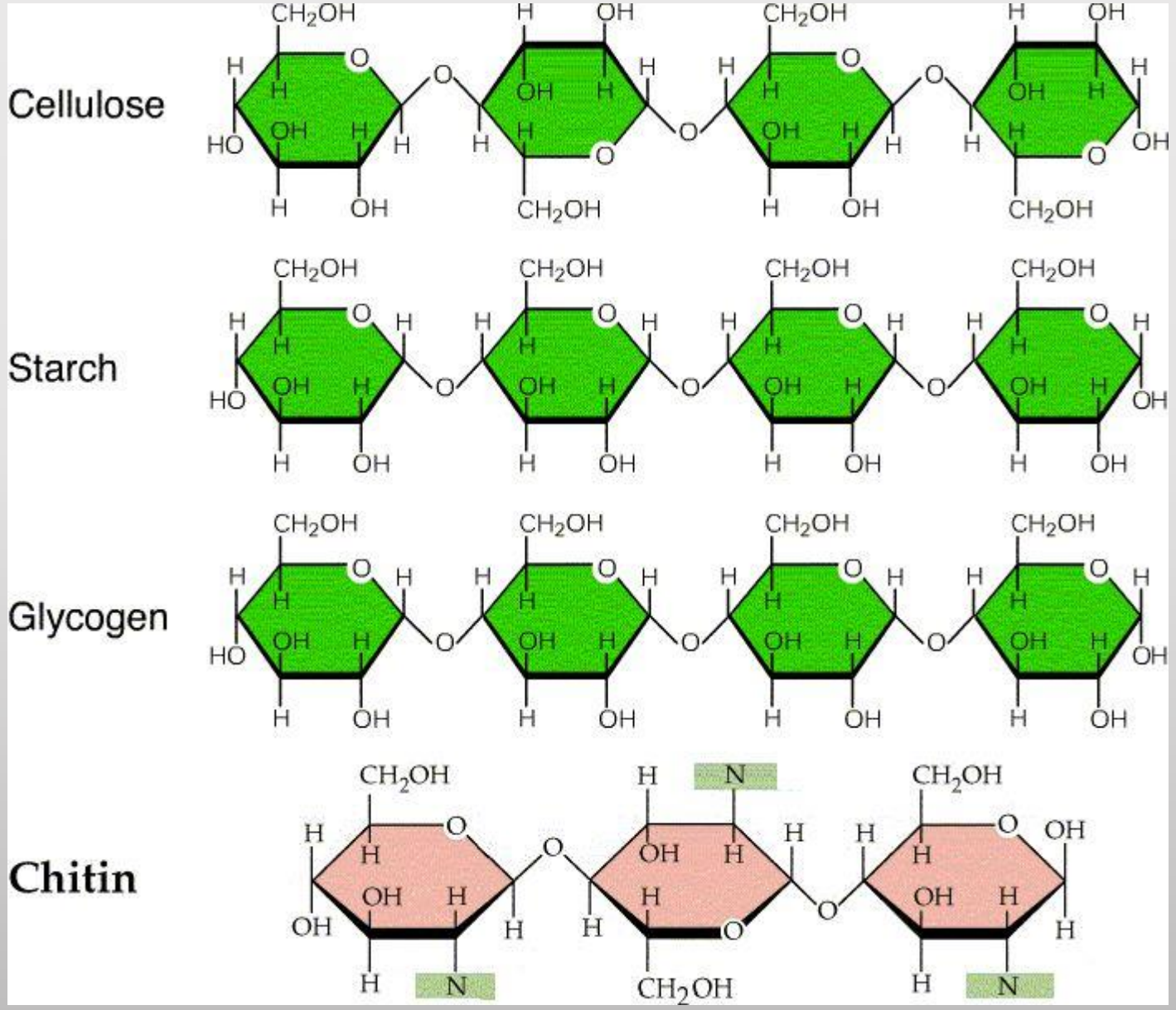
Maltose
Glucose and Glucose

Lactose isomers



Beta -Lactose is 1.05-1.22 sweeter than alpha–Lactose

Polysaccharides



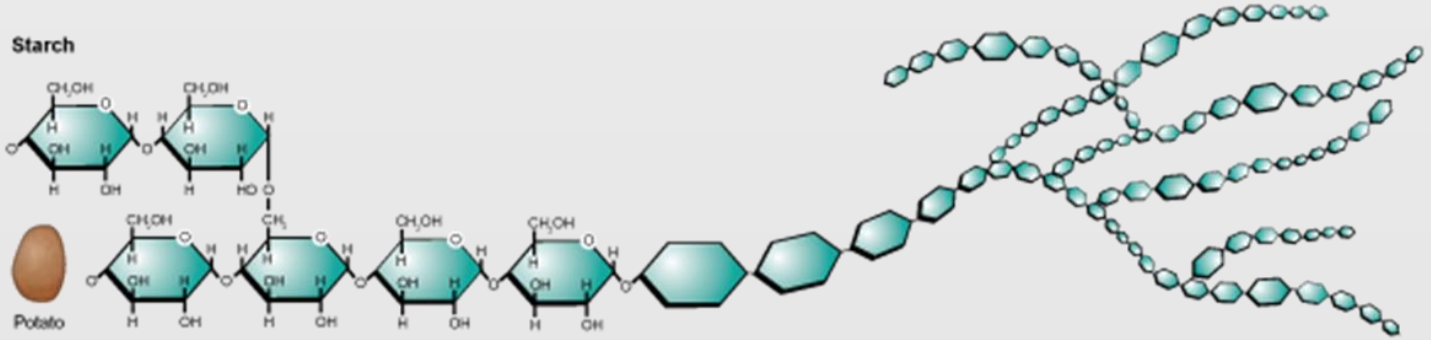
Cellulose is a ***glucose*** polymer polysaccharide in nature. The structural component of the cell wall -PAPERs

Starch is a ***glucose*** polymer produced by most green plants for energy storage

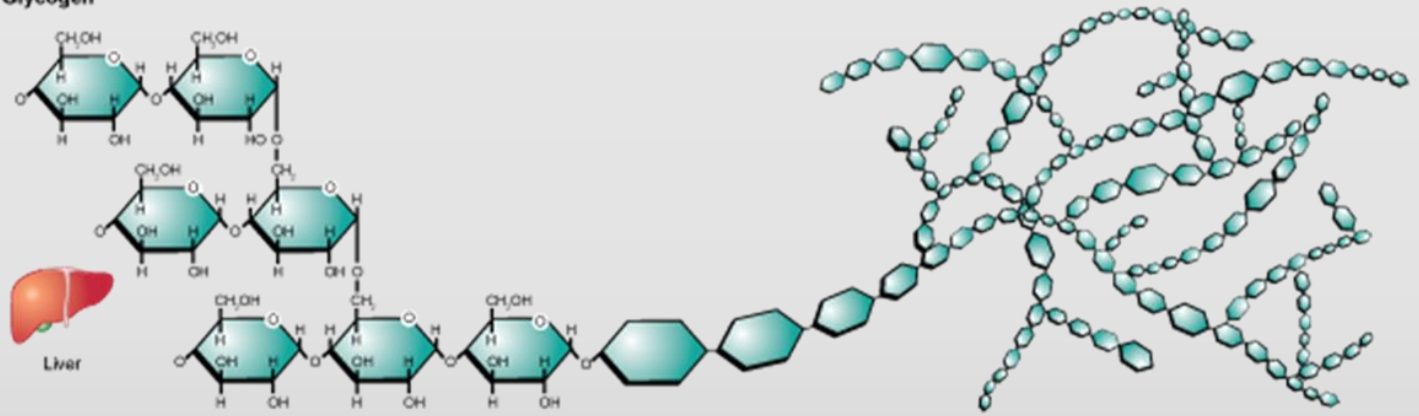
Glycogen is a ***glucose*** polymer is the primary energy source of the body

Chitin is an ***N-acetylglucosamine,*** an amide derivative of glucose, and **is** the 2nd most abundant polysaccharide in nature polysaccharide. in fungi & the exoskeletons of arthropods

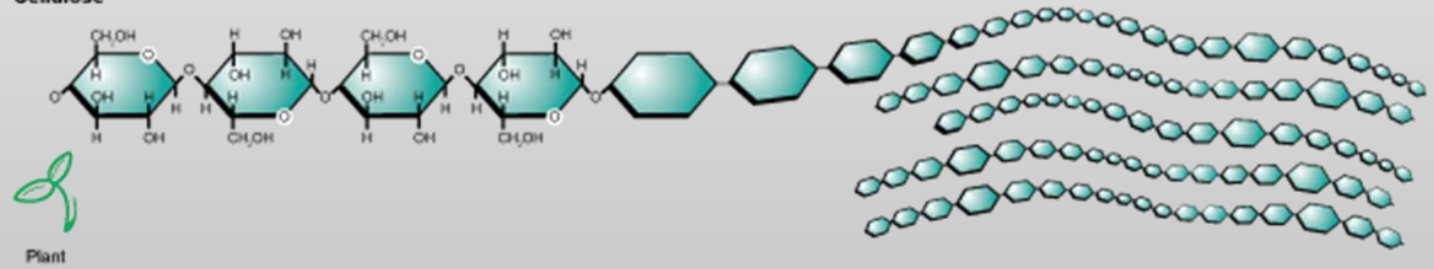
Starch



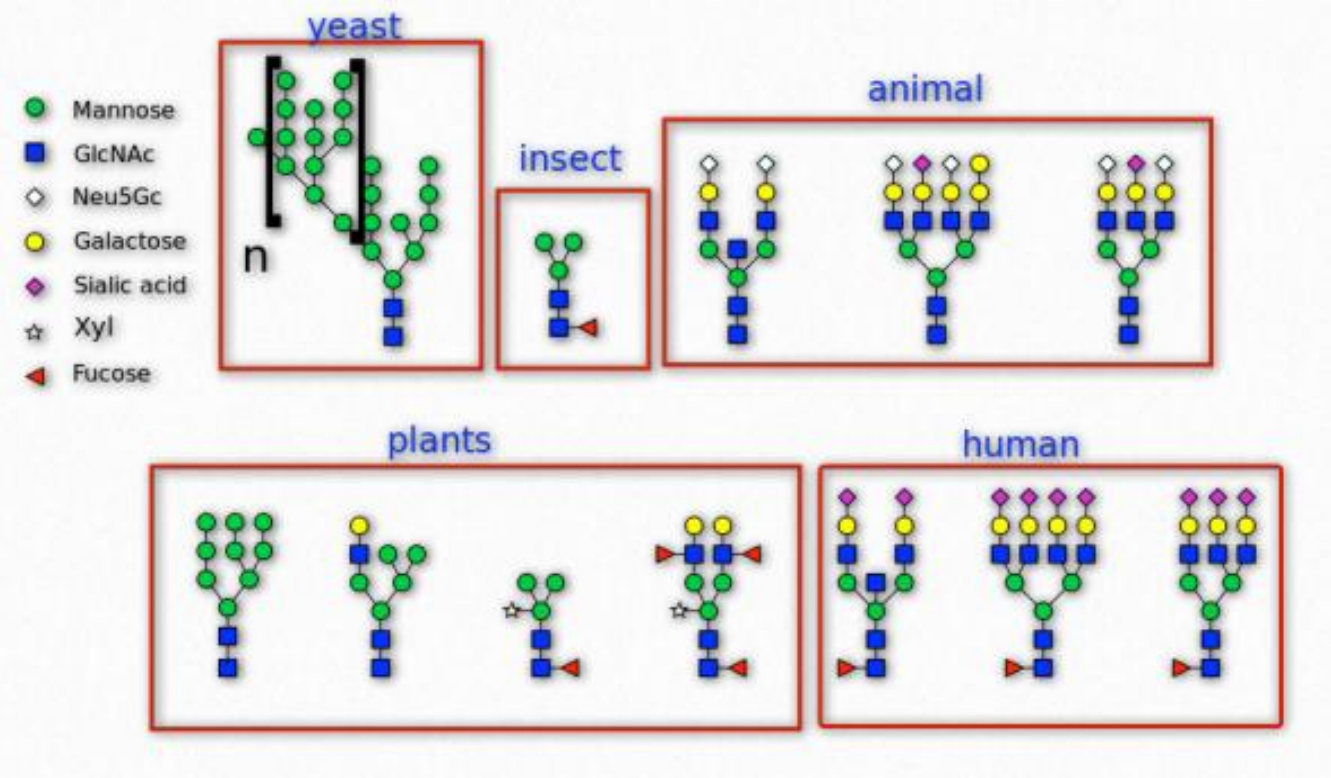
Glycogen



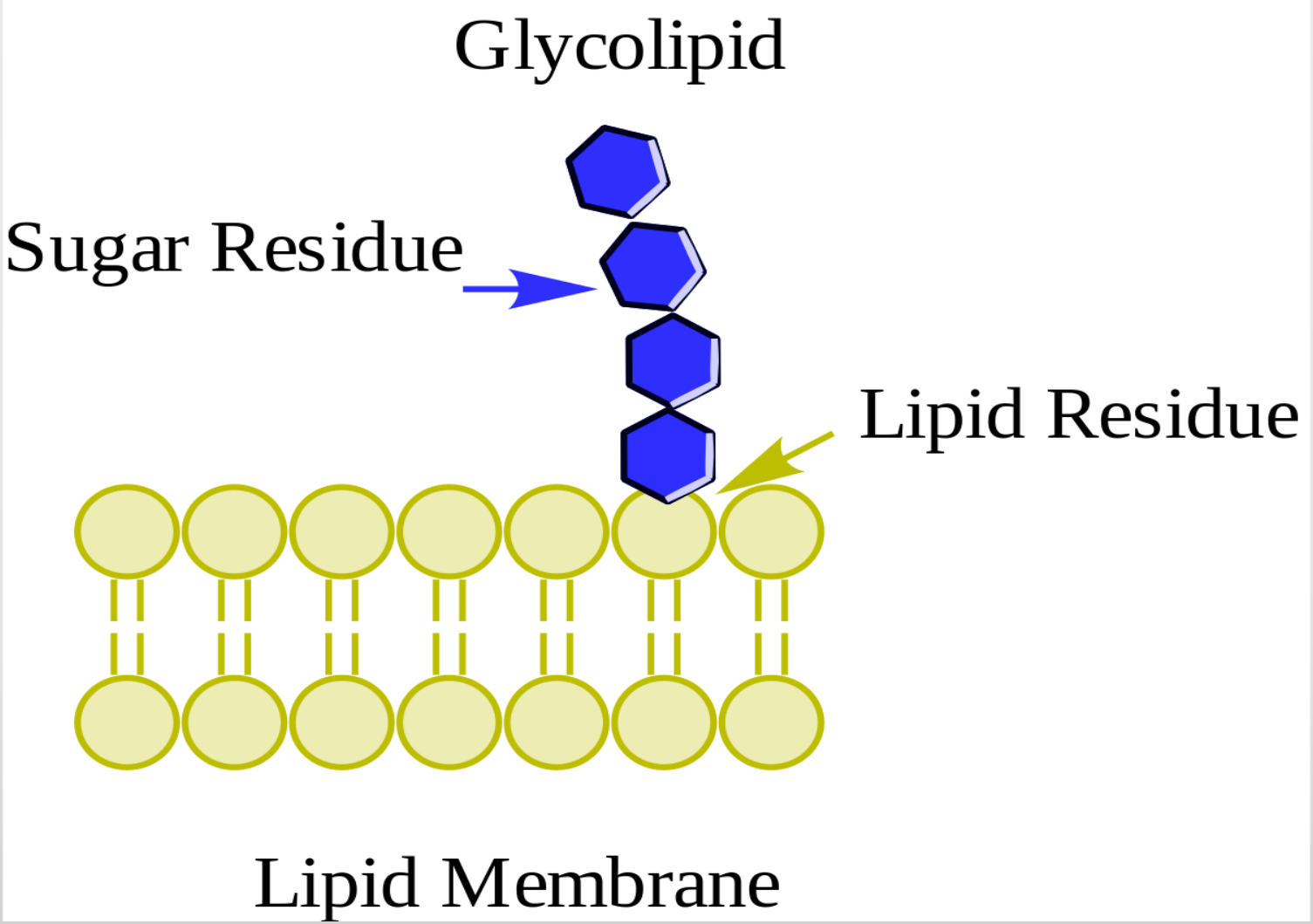
Cellulose



Carbohydrate+Proteins = Glycoproteins

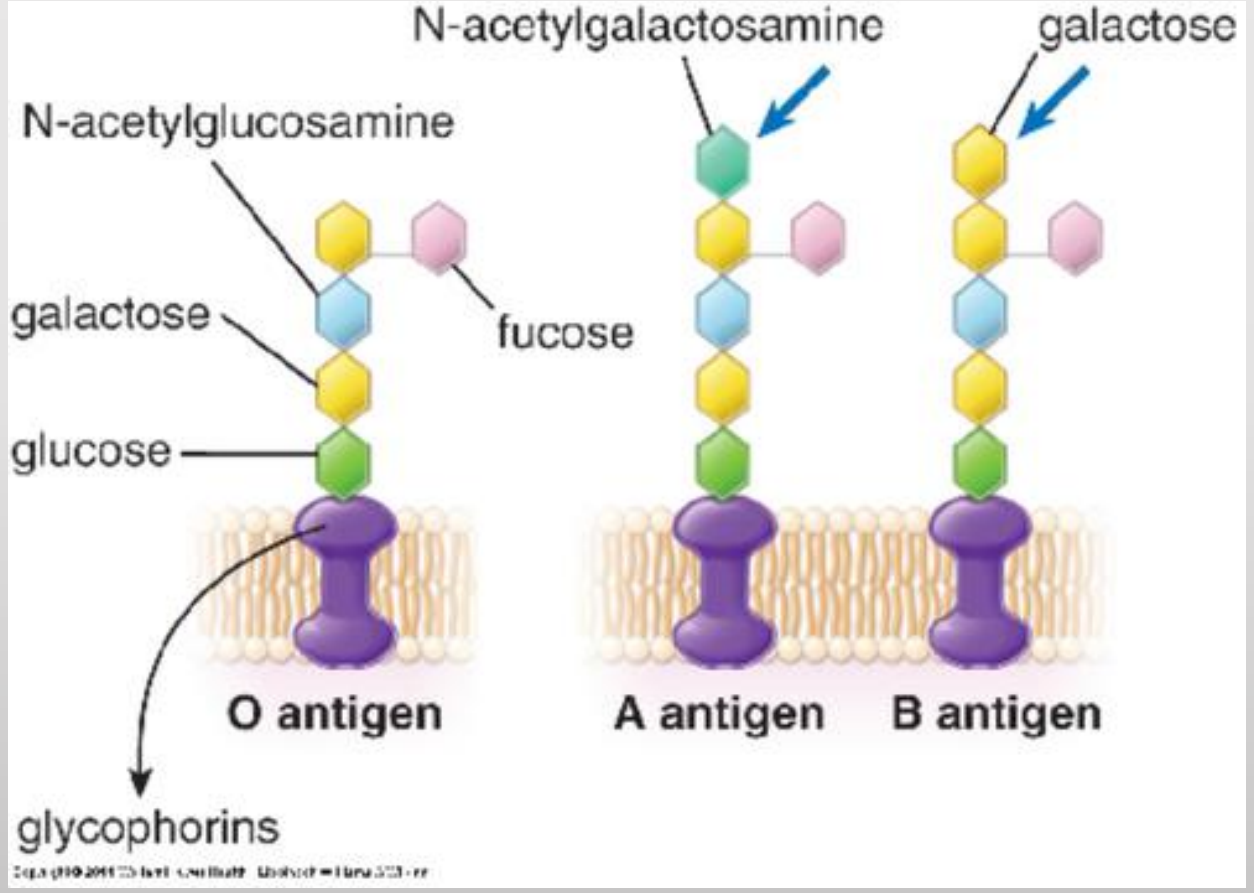


Glycoproteins are the group of proteins in which the oligosaccharide chains are covalently attached to the amino acid side chains or polypeptide backbones.



Glycolipids are components of cellular membranes comprised of a hydrophobic lipid tail and one or more hydrophilic sugar groups linked by a glycosidic bond.

Sugars and Blood Groups

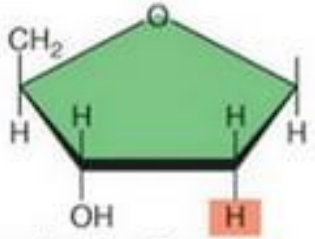


DNA vs. RNA

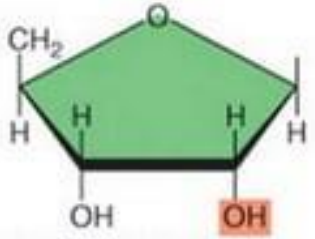
Double-stranded

Generally single-stranded

b.



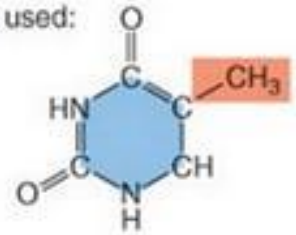
Deoxyribose as the sugar



Ribose as the sugar

c.

Bases used:

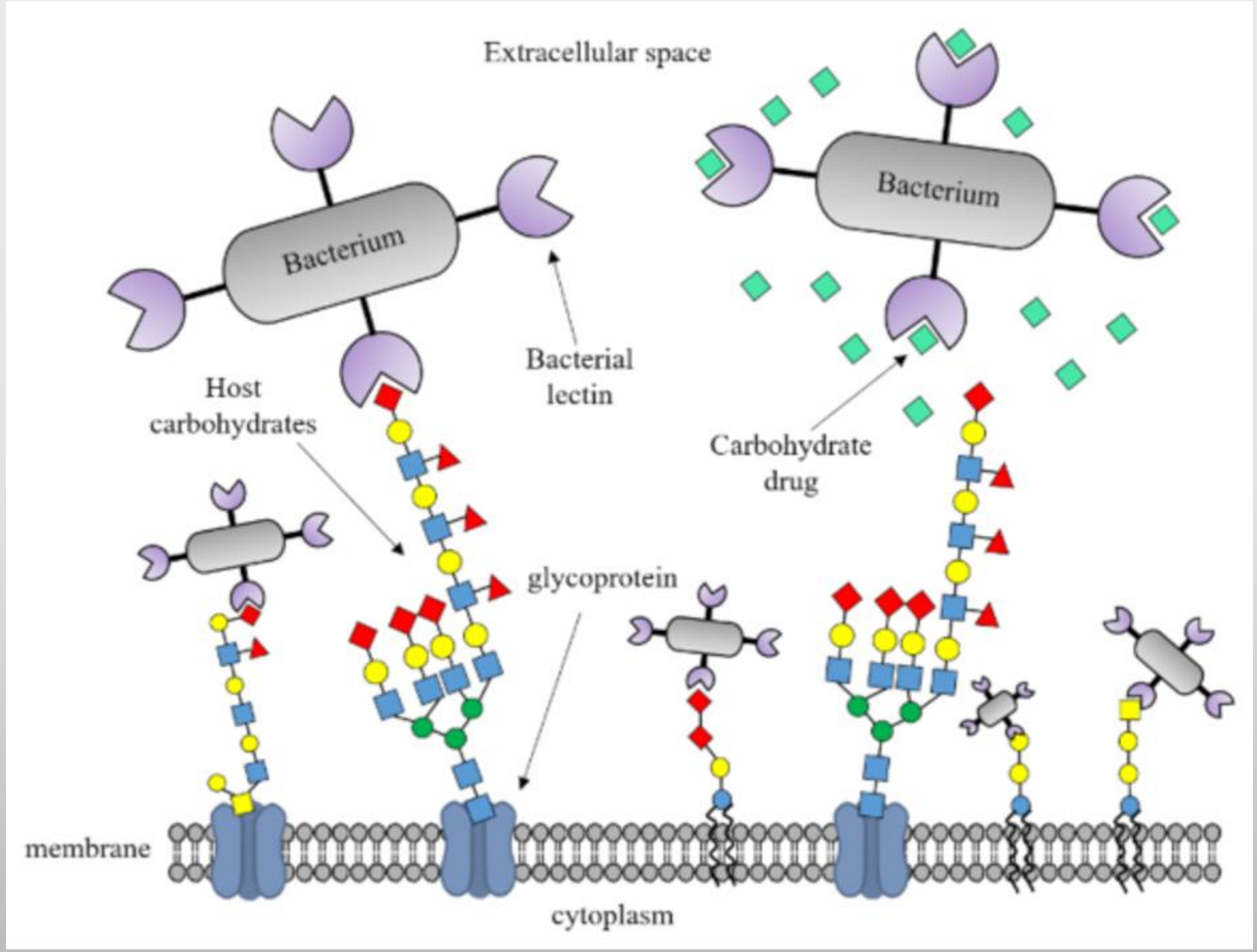


Thymine (T)
Cytosine (C)
Adenine (A)
Guanine (G)

Bases used:

Uracil (U)
Cytosine (C)
Adenine (A)
Guanine (G)

d.


Extracellular space
Bacterium
Bacterium
Bacterial lectin
Host carbohydrates
Carbohydrate drug
glycoprotein
membrane
cytoplasm

Gluten may act as a lectin with toxic properties for the intestinal cells. Gluten binds ‘high-mannose type’ glycoproteins and causes intolerance that is inhibitable by mannan.

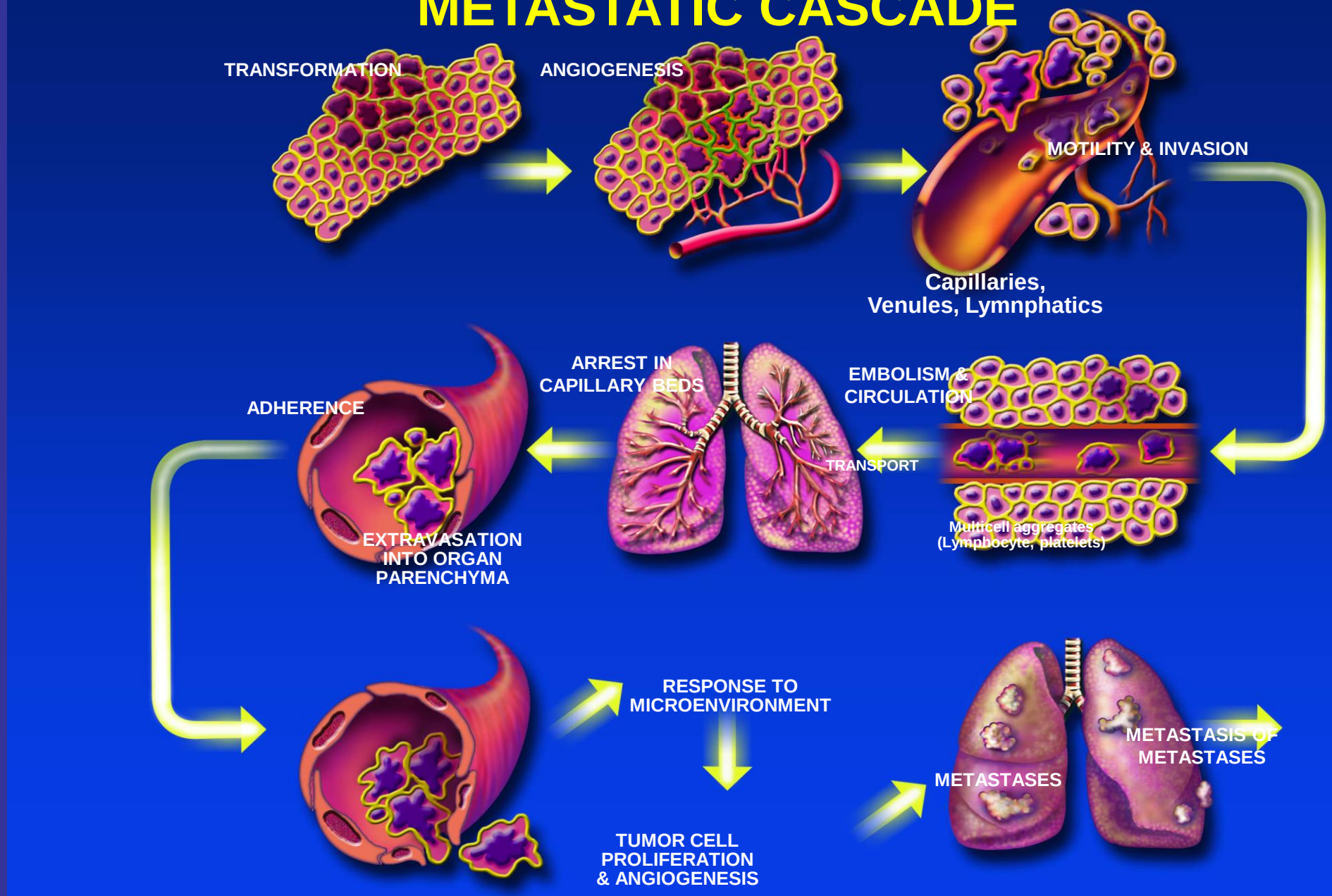
Ricin is a lectin and a highly potent toxin produced in the seeds of the castor oil plant, Ricinus communis.

C-type lectin-like proteins are the hemorrhagic components in snake venom.

TUMOR METASTASIS

THE MOST DEVESTATING ASPECT OF CANCER

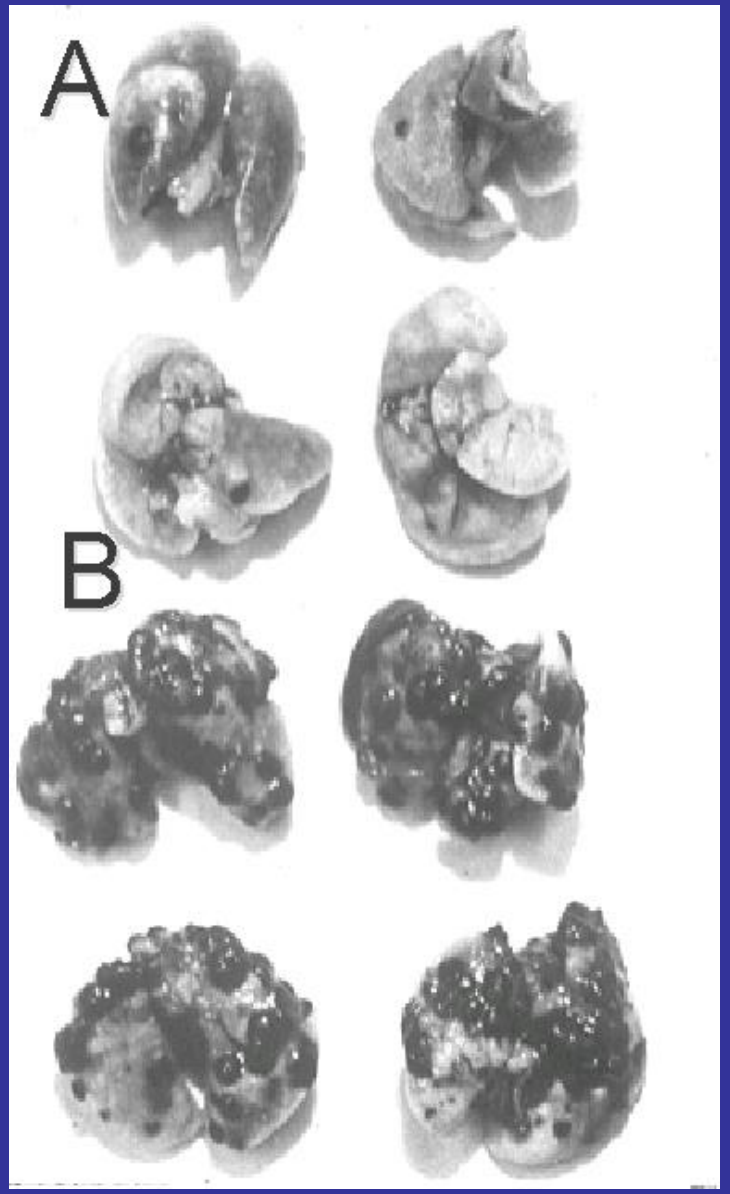
METASTATIC CASCADE



What Mediates Tumor Cell Embolism?

Andrée in 1874 was one of the first to describe Tumor Embolism of the pulmonary arteries following invasion of systemic veins

Low & High Metastatic Cell Clones



The Birth of a Research Field

What Mediates Tumor Cell Embolism?

Carbohydrate Recognition !

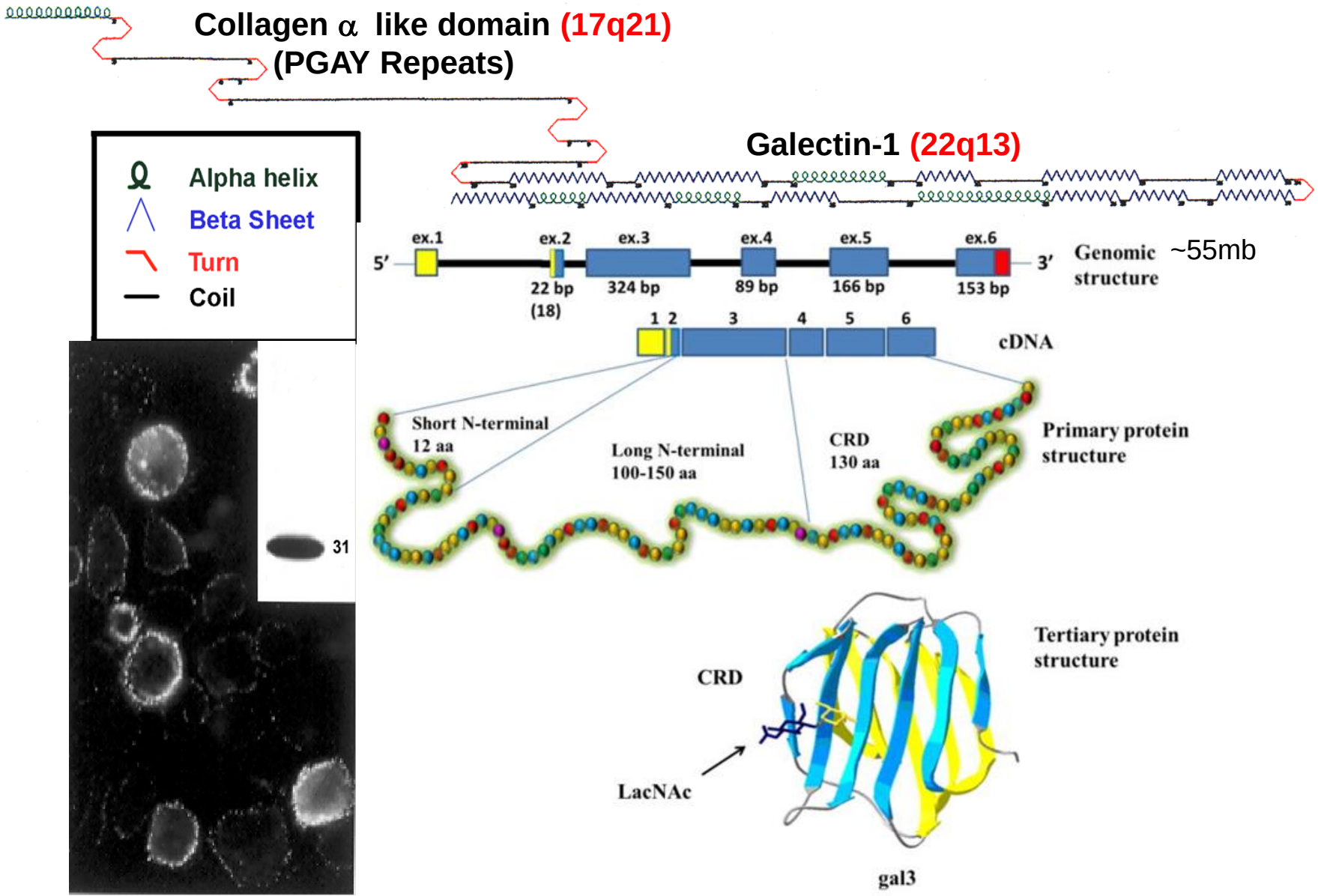
*Raz A and Lotan R. **Lectin-like** activities associated with human and murine neoplastic cells. Cancer Res. 1981; 41 :3642-7.*

GALECTINs

In 1994 we recognized it as a gene family

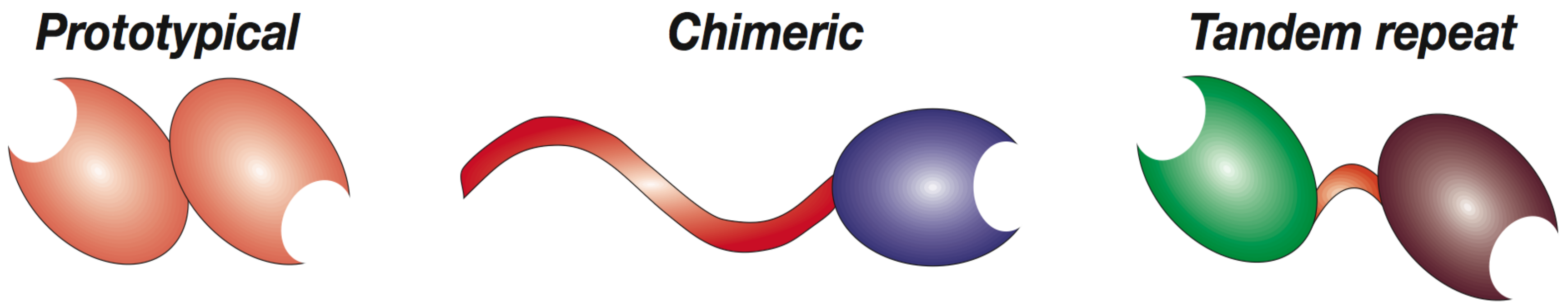
Family of Carbohydrate-Binding Proteins Sharing a Conserved Sequence of the Sugar-Binding Motif and Affinity for Galactoside Containing Glycoconjugate

Galectin-3 - A Chimera Protein (14q21-22)



a

Galectins in humans



Galectin-1
Galectin-2
Galectin-7
Galectin-10
Galectin-13
Galectin-14

Galectin-3

LGALS3

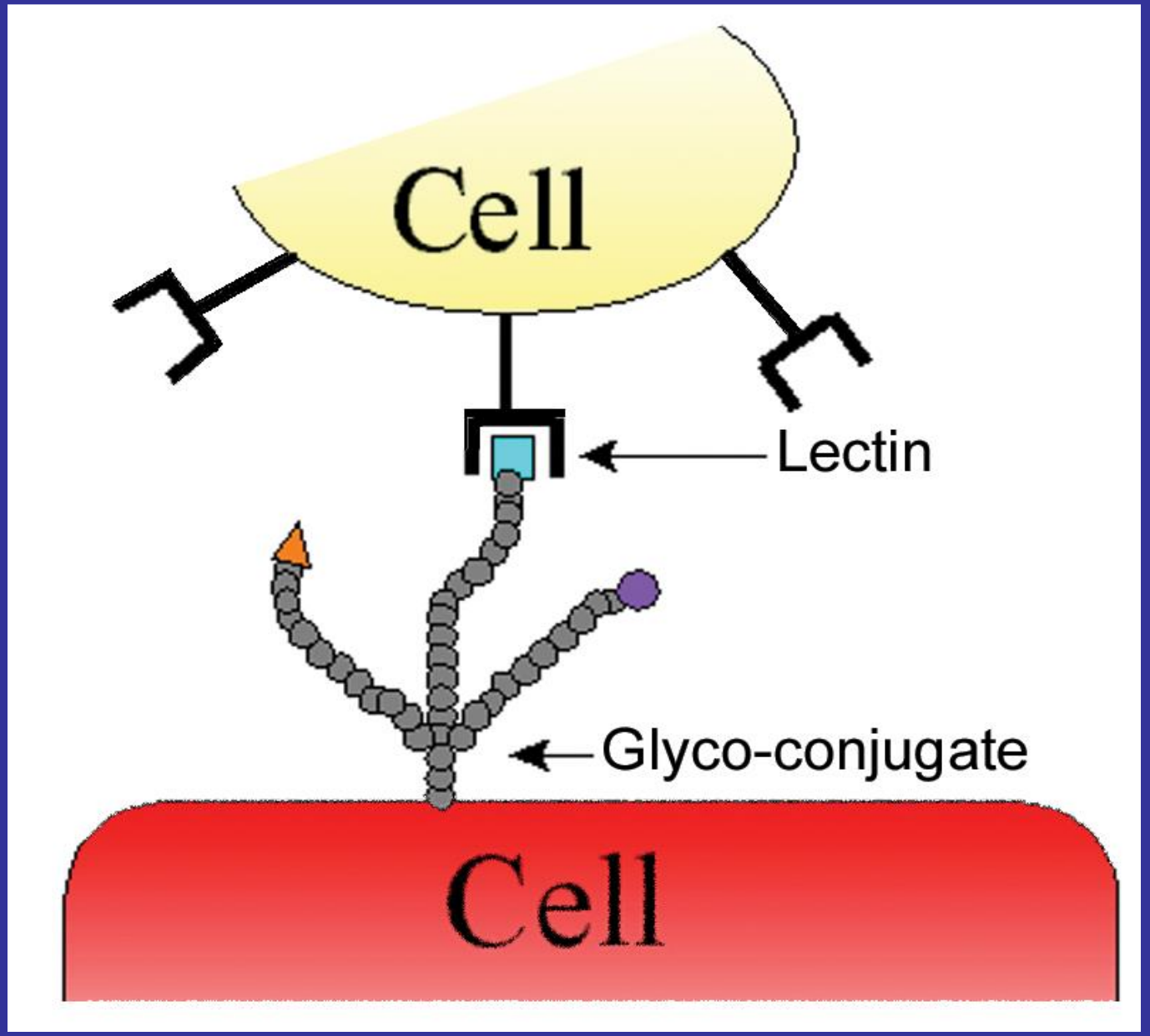
Galectin-4
Galectin-8
Galectin-9
Galectin-12

Raz A, Pazerini G, Carmi P (1989) Identification of the metastasis-associated, galactoside-binding lectin as *a chimeric gene* product with homology to an IgE-binding protein. Cancer Res. 49:3489-93.

b

Sequence alignments of some human galectins

```
              41    *  *  *                    56      *     66    *   71*  *
Galectin-1   -NLCLHFNPRFNAHGD------ANTIVCNSKD-GGAWG—TEQRE-
Galectin-2   -KLNLHFNPRFS----------ESTIVCNSLD-GSNWG-QEQRE-
Galectin-3   -DVAFHFNPRFNENN-------RRVIVCNTKL-DNNWG-REERQ-
Galectin-4   -DVAFHFNPRFDG---------WDKVVFNTLQ-GGKWG-SEERK- (N-term)
             -DIALHINPRMG----------NGTVVRNSLL-NGSWG-SEEKK- (C-term)
Galectin-7   -DAALHFNPRLD----------TSEVVFNSKE-QGSWG-REERG
```


Cell
Lectin
Glyco-conjugate
Cell

What is the Biological consequence of Galectin-3 Inhibition?

Optimal Sugar Inhibitor

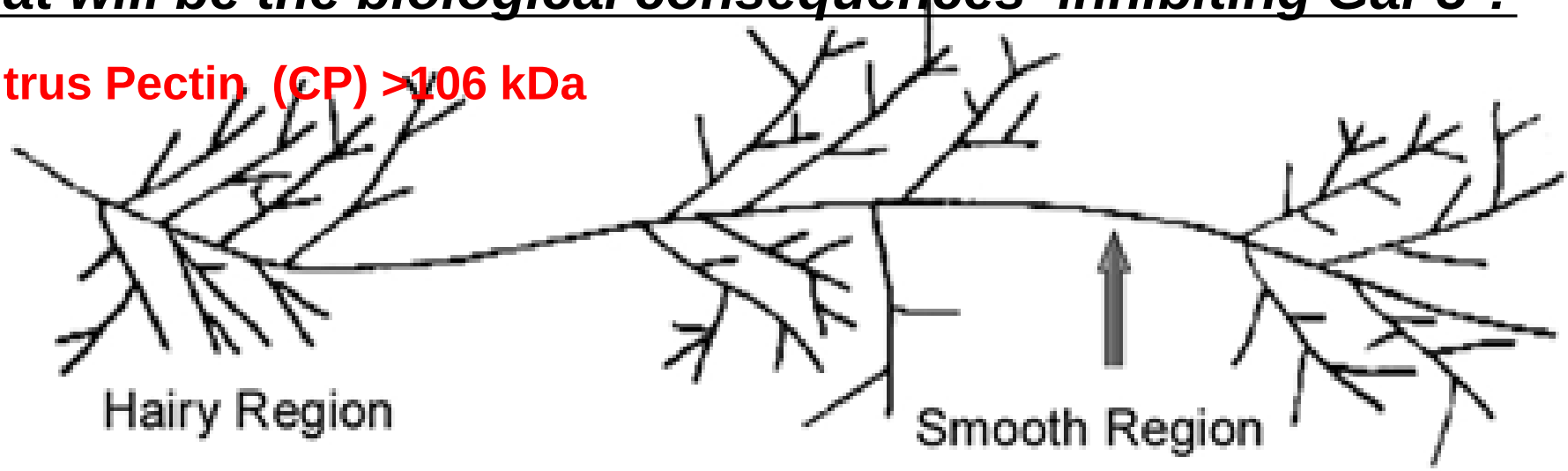
1- *Rich in Galactose Residues*
2- *Water Soluble*
3- *Extended Half-Life in the Circulation*


Application of pectin
Dairy products
Bakery
Jam and Jelly
Antioxidant activity
Prebiotic
Pharma-ceuticals
Coating and film

What will be the biological consequences inhibiting Gal-3 ?

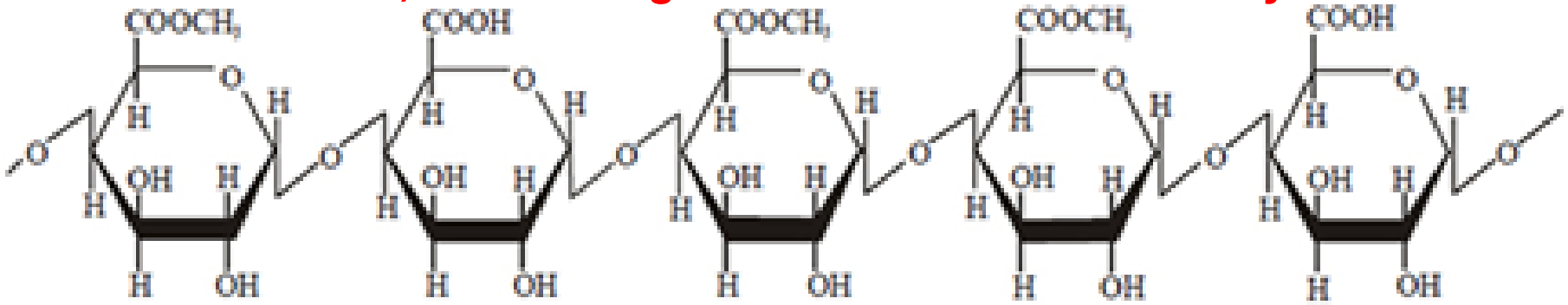
Citrus Pectin (CP) >106 kDa

I



Linear Backbone: 1, 4-linkedD-galacturonic acid & its methyl ester

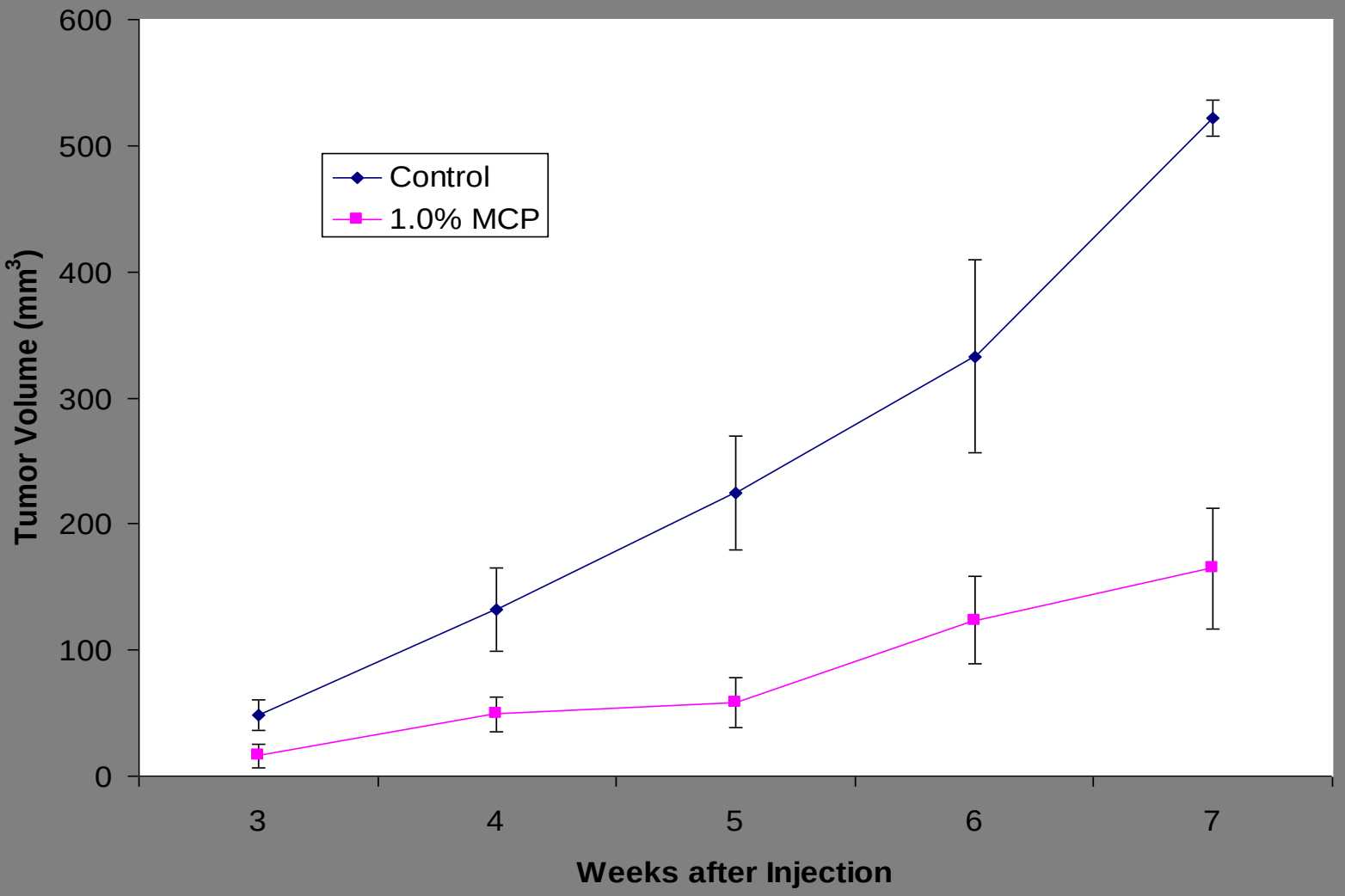
II



Modified Citrus Pectin (MCP) ~0.5-104 kDa

III

Tumor Growth

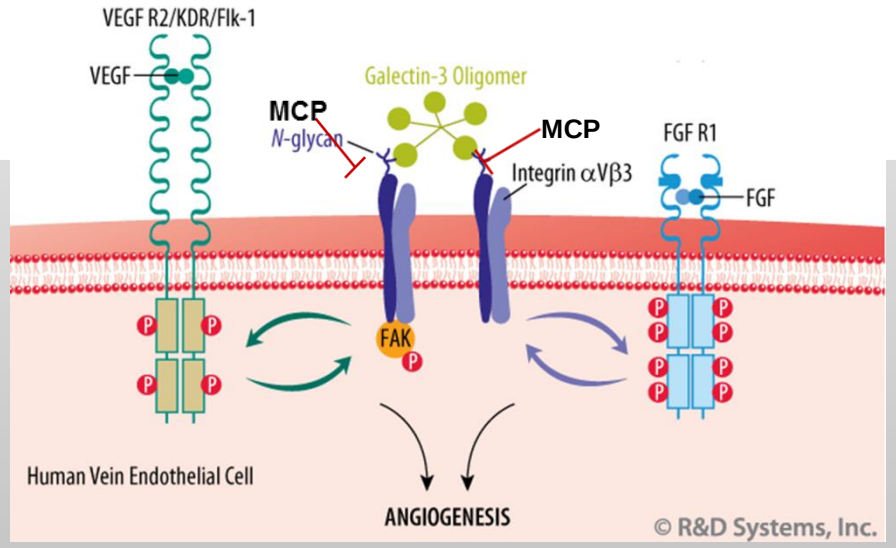


The Effect of Oral MCP on Lung Metastasis of Human Breast Carcinoma Cells form the Mammary Fat Pad of Nude Mice

Angiogenesis

Control

MCP



This work was Patented: US Patent No: 5,895,784: Method for Treatment of Cancer by Oral Administration of Modified Pectin and licensed for $1,000,000.

I was awarded the "MERIT Award" by the Division of Cancer Biology, National Institute of Health, National Cancer Institute, {(R37CA046120-19)(First from the State of Michigan)].

Human and Tumor Galectin 3

(From the Bench to the Clinic and Back)

Diagnosis/Prognosis

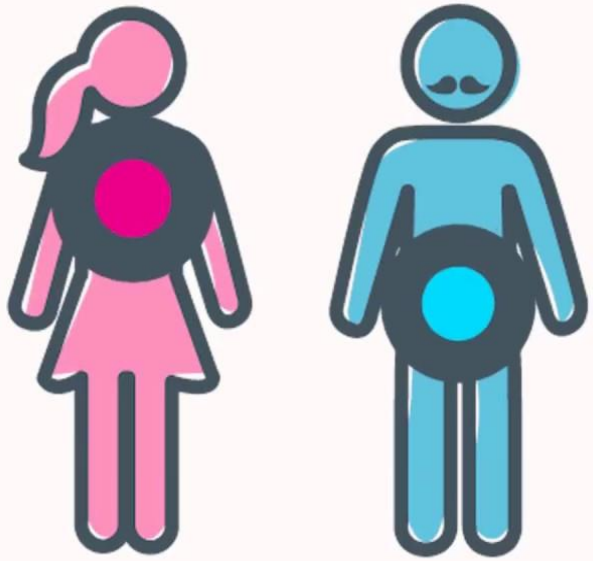
Thyroid ***(Ad - →Ca +)***

Therapy

~ 60 Clinical trials

(Gal-3 Antagonist)

What do breasts and prostates have in common?



COLLAGENASE CLEAVAGE SITES OF GALECTIN-3

[1]MADNFSLHDALSGSGNPNPQGWPGAWGNQPAG AGGYPGAS[40]

[41]YPGAYPGQAPPGAYPGQAPPGA YH GAPGAYPGAPAPGVYP[80]

[81]GPPSGPGAYPSSGQPSAPGAYPATGPYGAPAGPLIVPYNL[120]

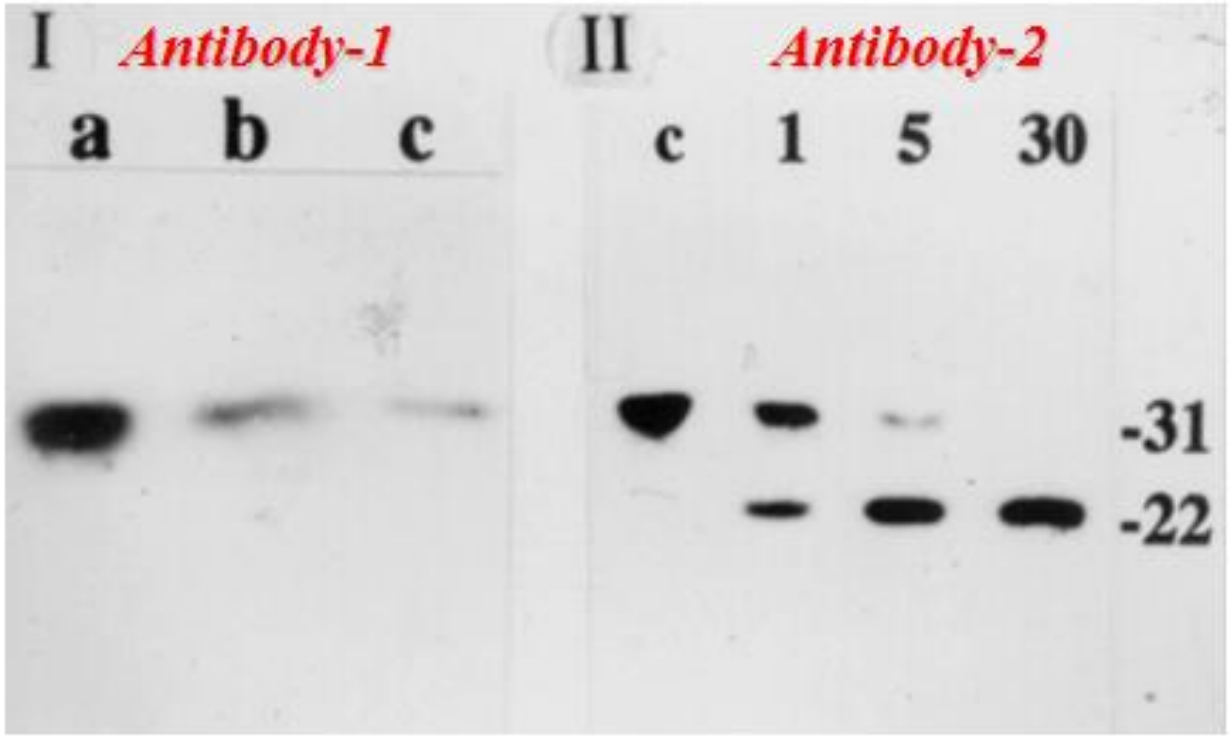
[121]PLPGGVVPRMLITILGTVKPNANRIALDFQRGNDVAFHFN[160]

[161]PRFNENNRRVIVCNTKLDNNWGREERQSVFPFESGKPFKI[200]

[201]QVLVEPDHFKVAVNDAHLLQYNHRVKKLNEISKGISGDI[240]

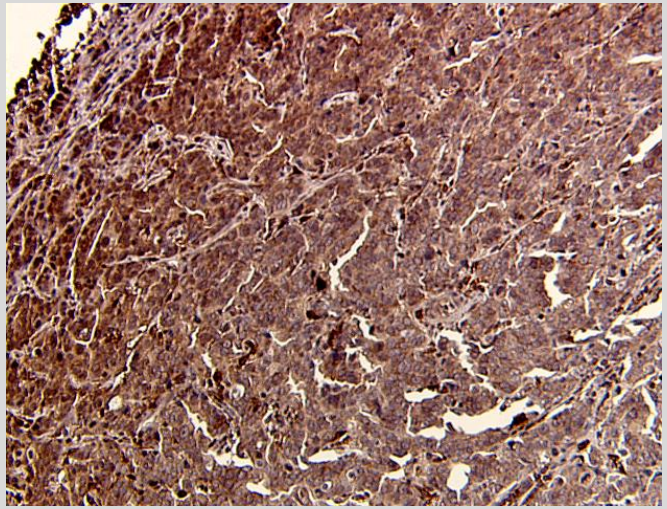
[241]DLTSASYIMI

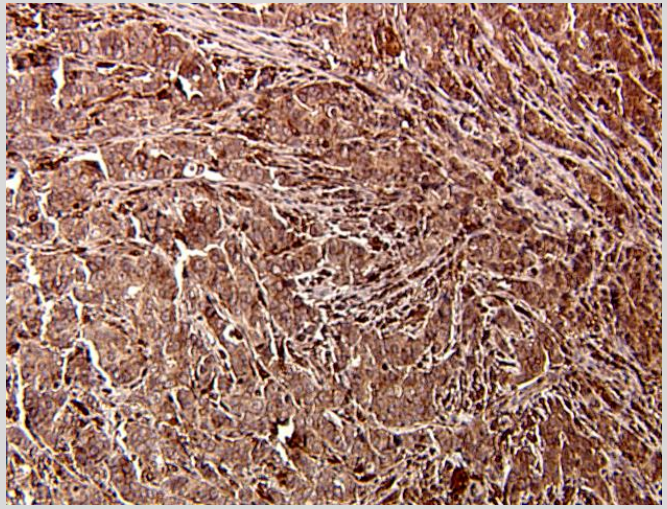
Detection of MMP-9 cleaved Gal-3 product



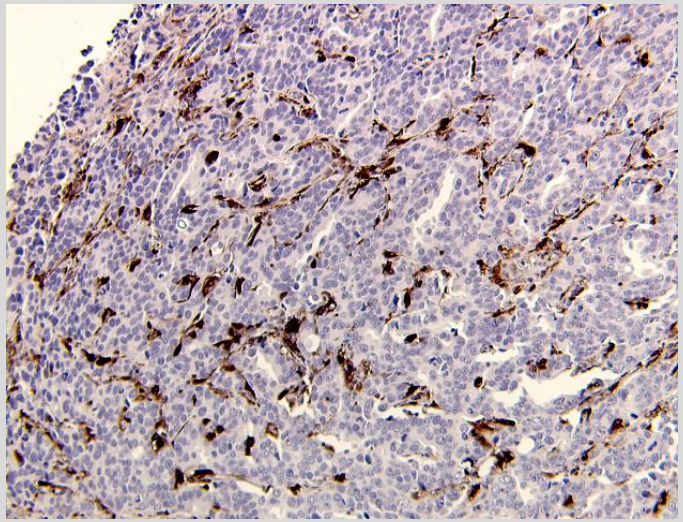
Breast Tumor

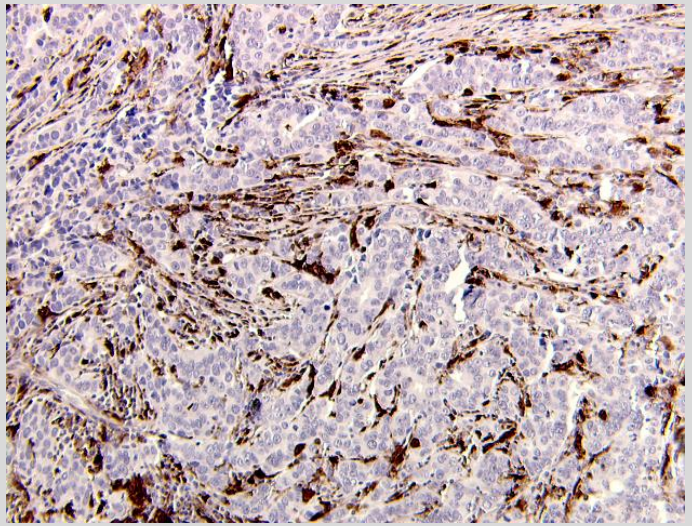
Anti-galectin-3
(degraded)



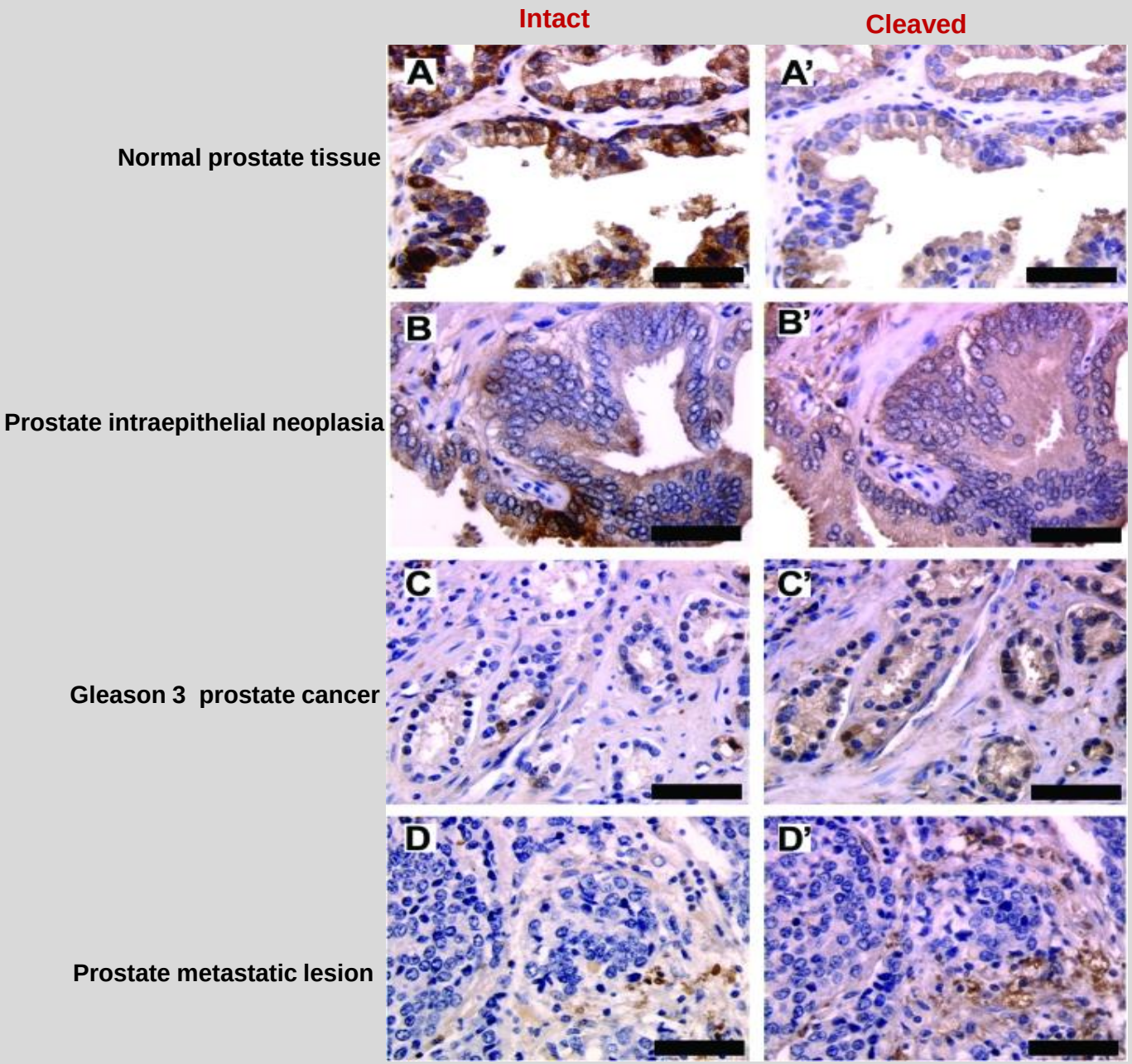


Anti-galectin-3
(intact)





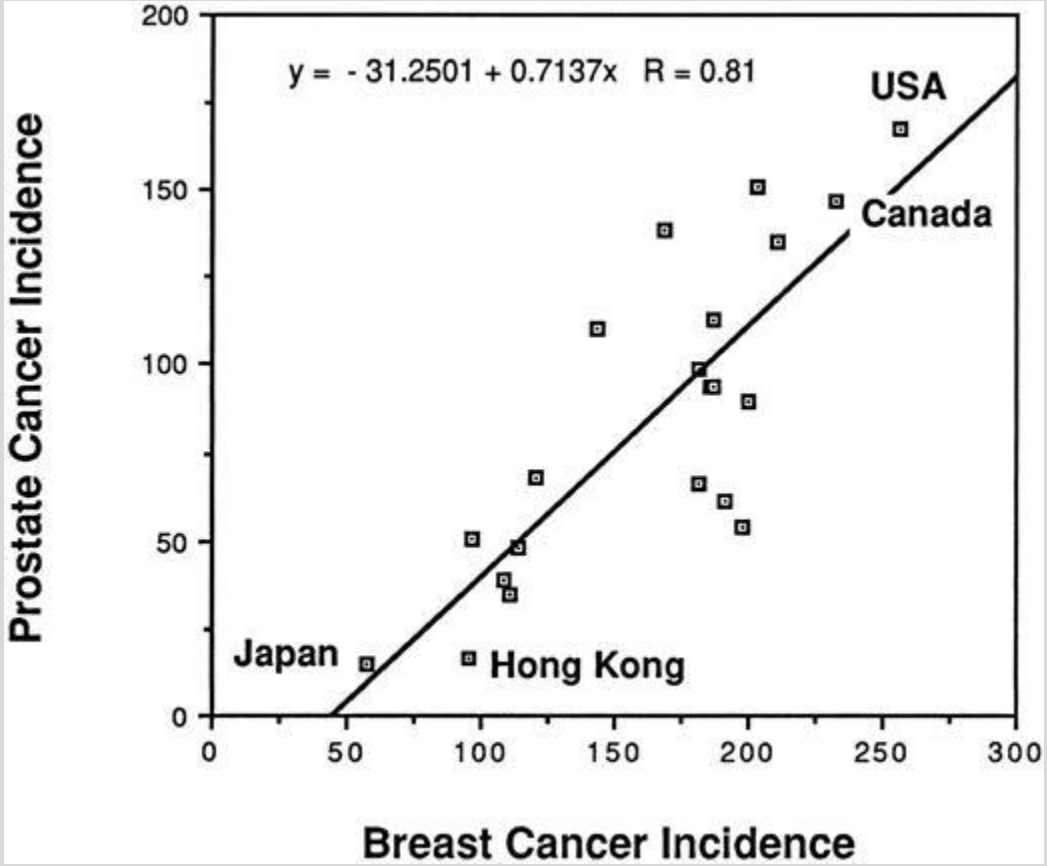
Galectin-3 expression in prostate cancer progression



Breast and Prostate cancers: more similar than different

Commonality between breast and prostate cancer provides a unique opportunities for new forms of hormone therapy that take advantage of the persistent steroid- and receptor-dependence of these cancers for growth and survival.
Risbridger G.P., *et al*., *Nature Rev. Cancer* 10: 205 (2010)

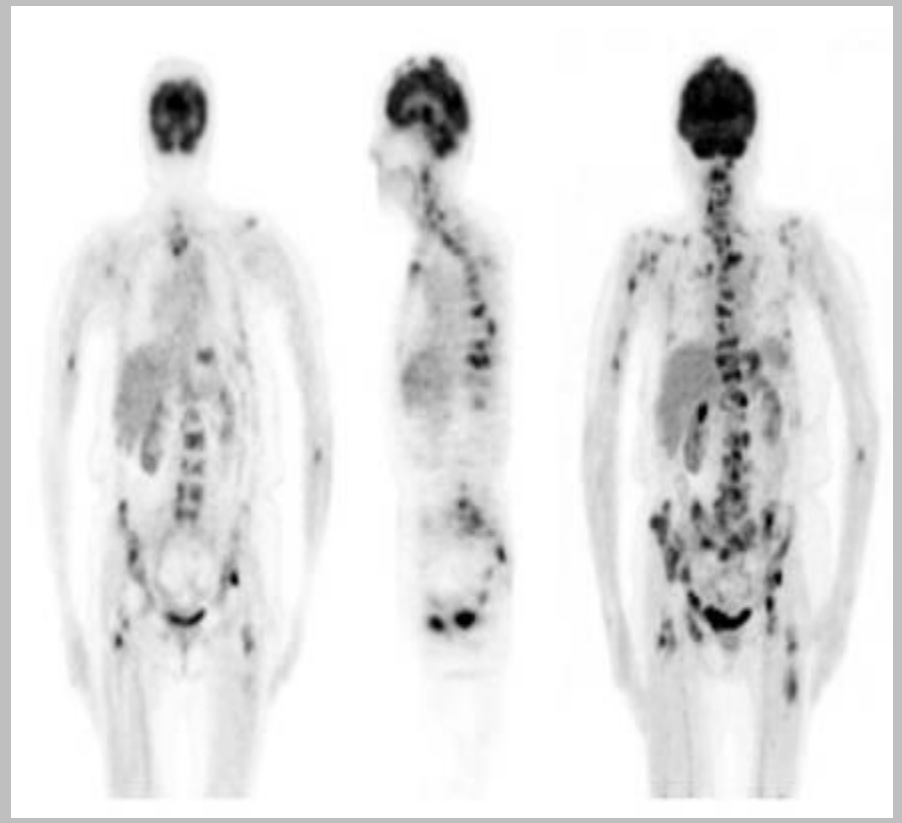
The incidence of metastatic prostate cancer has stabilized at a rate now similar to that seen in breast cancer. This finding suggests a similarity between the two diseases.
Welch, H.G., *et al., N Engl J Med*. 73:1685 (2015).



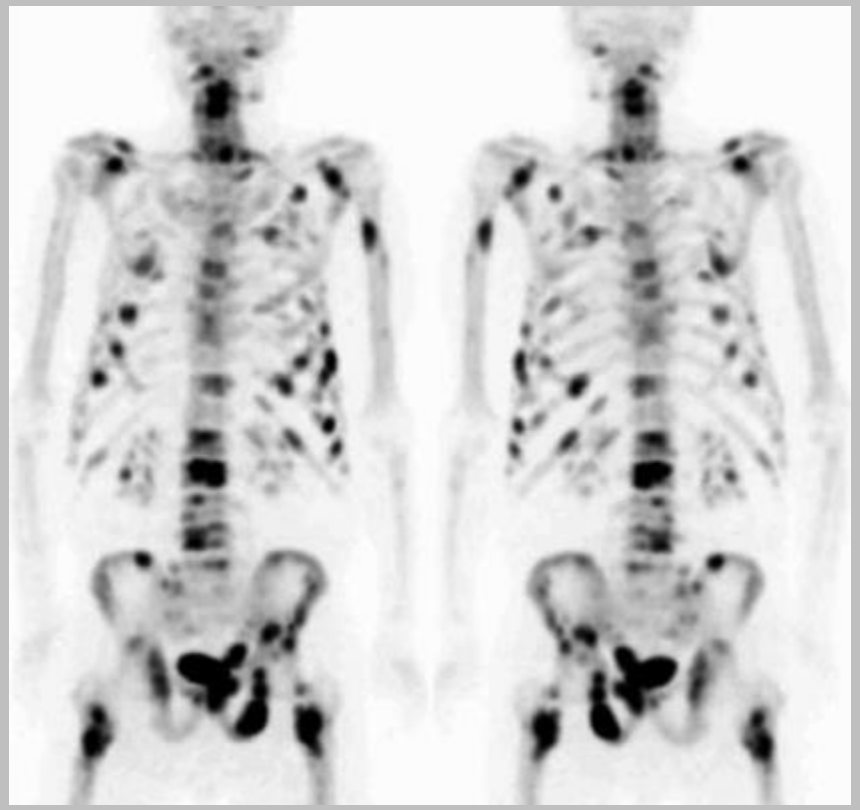
Correlation between breast cancer and prostate cancer incidence rates in 21 countries
López-Otín,C., *et al.,* Endocrine Reviews; 19: 365 (1998)

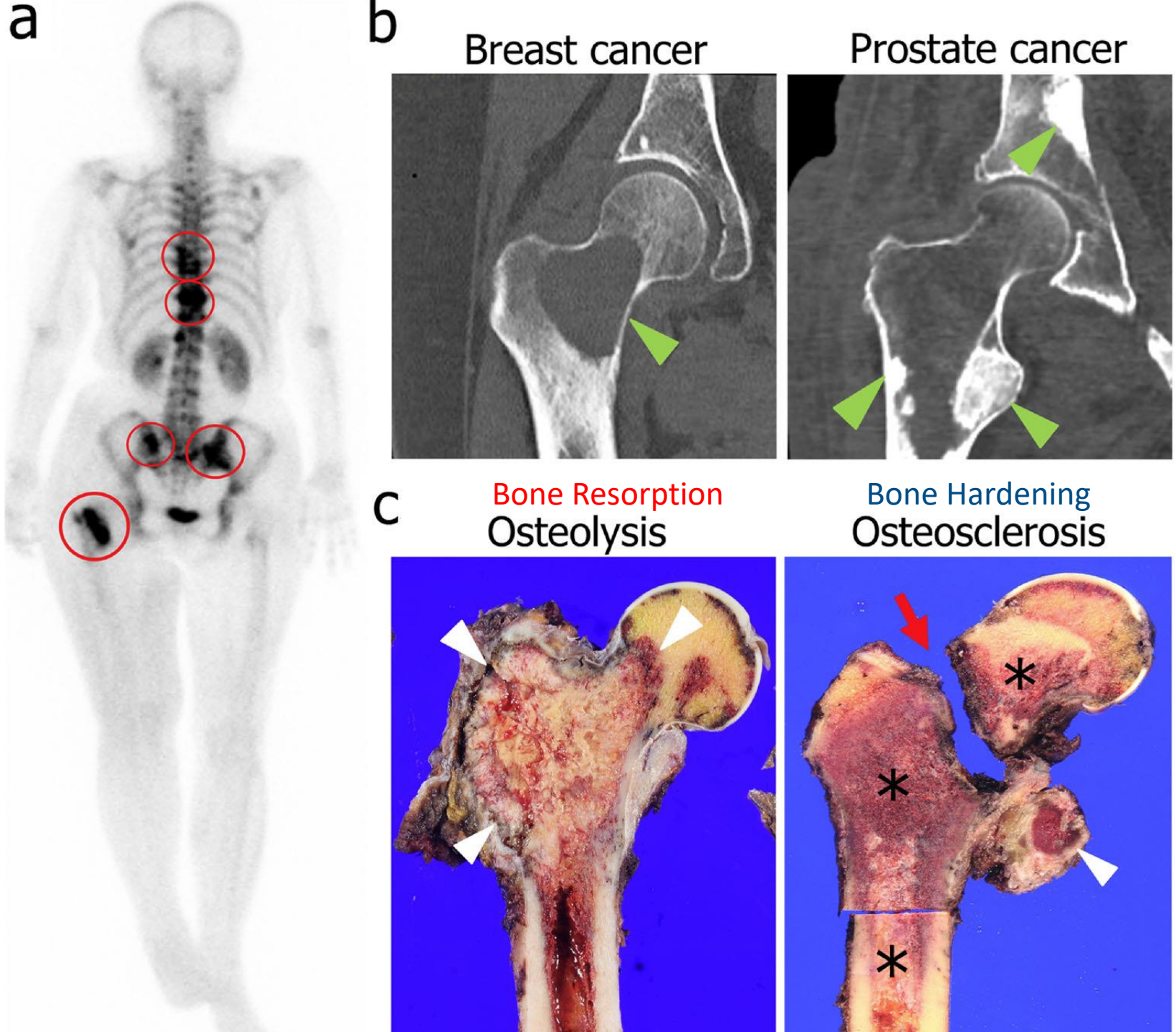
Cancer Bone Scan

Breast

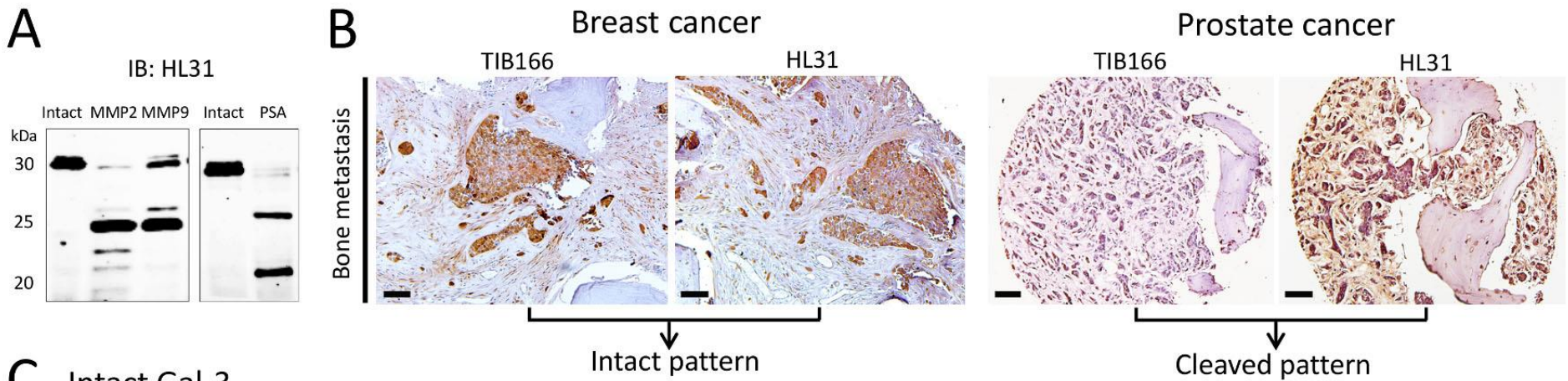


Prostate




a
b
Breast cancer
Prostate cancer
c
Bone Resorption
Osteolysis
Bone Hardening
Osteosclerosis

Galectin-3 Expression in Clinical Samples of Human Breast & Prostate Metastatic Growth in the Bone



C

Intact Gal-3

Metastasis	Pattern	Breast	Prostate	OR (95% CI)	P value	Adjusted p value
Bone	Intact pattern	13 **(76%)**	10 **(13%)**	0.048 (0.010,0.194)	<0.001	**<0.001**
	Others	4 (24%)	67 (87%)	Reference		

Cleaved Gal-3

Metastasis	Pattern	Breast	Prostate	OR (95% CI)	P value	Adjusted p value
Bone	Cleaved pattern	2 **(12%)**	57 **(74%)**	20.594 (4.234,200.793)	<0.001	**<0.001**
	Others	15 (88%)	20 (26%)	Reference		

Table 1.

Therapeutic Drugs for Bone Metastases

Cancer type	Drug	
Prostate	Zoledoronic acid	Bisphosphonate
	Denosumab	RANKL inhibitor
Breast	Zoledoronic acid Denosumab	
Lung	Zoledoronic acid Denosumab	
Other solid tumors (Renal;Bladder;Thyroid;Liver; Gastric; Colorectal)	Zoledoronic acid Denosumab	

Base on the above we have suggested that *Galectin-3* could serve as a beacon for individual skeletal metastasis management