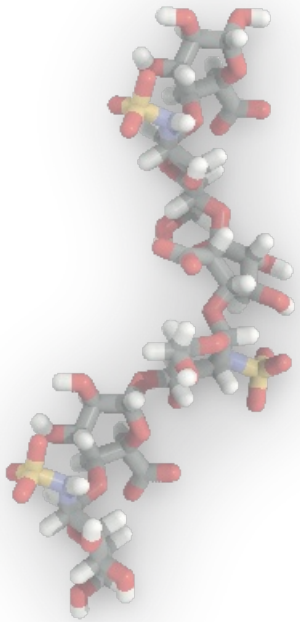


Decoding sugar messages to create new diagnostics and therapeutics

Mia Huang, PhD

Associate Professor

miahuang@scripps.edu

Scripps Research Chemistry

Scripps Research Molecular Medicine

Metro Manila, Philippines

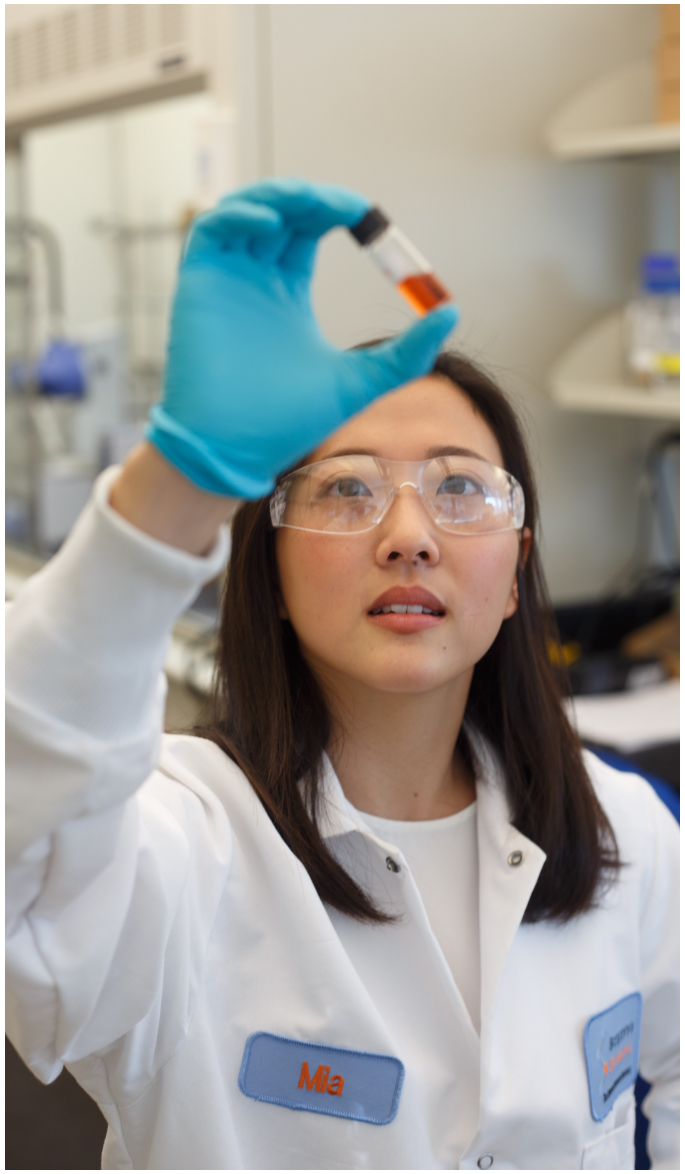
voted second worst traffic in the world

worst city to drive in the world (BBC)

Mia Huang, Ph.D.

Associate Professor
Department of Chemistry

- **B.A. Chemistry, 2007**
  City University of New York Queens College
- **Ph.D. Chemistry, 2012**
  New York University
- **Postdoctoral Fellow, 2013**
  Yale University
- **NIH Glycosciences Postdoc, 2018**
  UC San Diego
- **Assistant Professor (2018-2021)**
- **Associate Professor (2022-)**
  2023 Alfred P. Sloan Research Fellowship in Chemistry
  2023 David Y. Gin Investigator Award in Carbohydrate Chemistry
  2021 Maximizing Investigators' Research Award, NIH

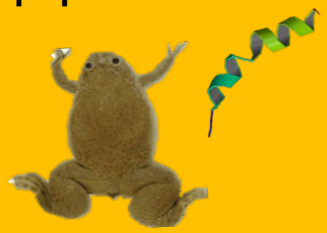


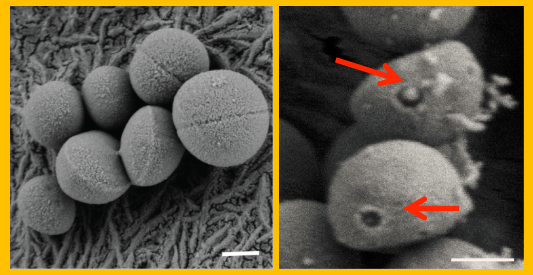
choosing chemistry, the central science

- Understand life at the molecular level
- Develop molecular solutions to intervene in disease
- Discover new applications
- Versatile biological knowledge

PhD work: biomimetic materials

antimicrobial peptides

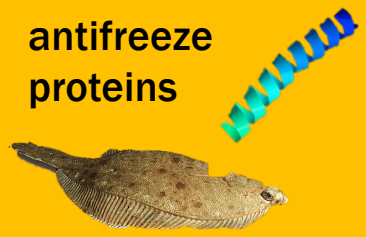




antibiotics against resistant infections

extract chemical mechanisms of function

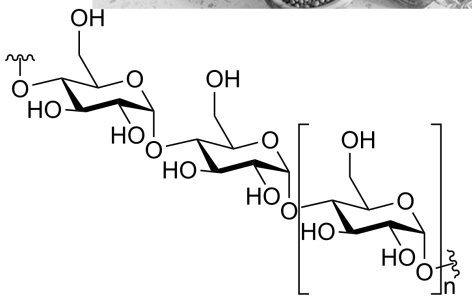
antifreeze proteins



cryoprotectants to preserve tissues

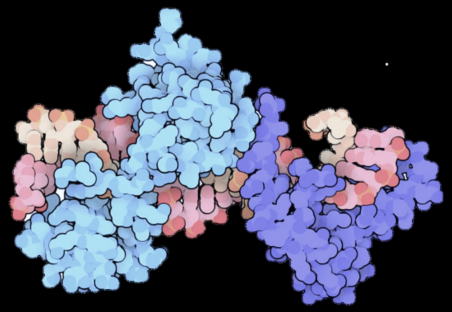
sugars | glycans

nutrition vs information

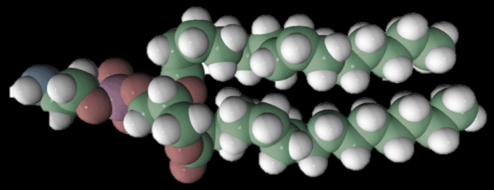


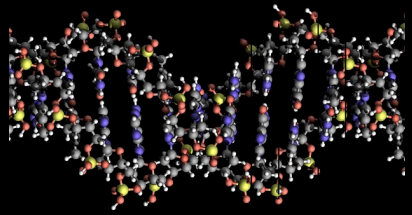
glycans are among the biomolecules of life

proteins

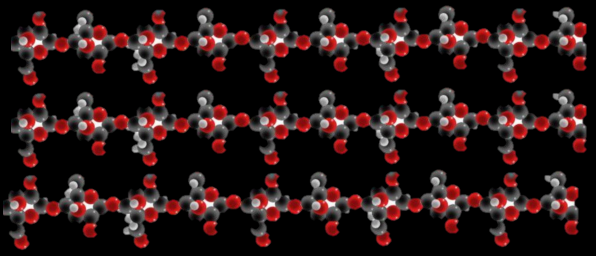


lipids



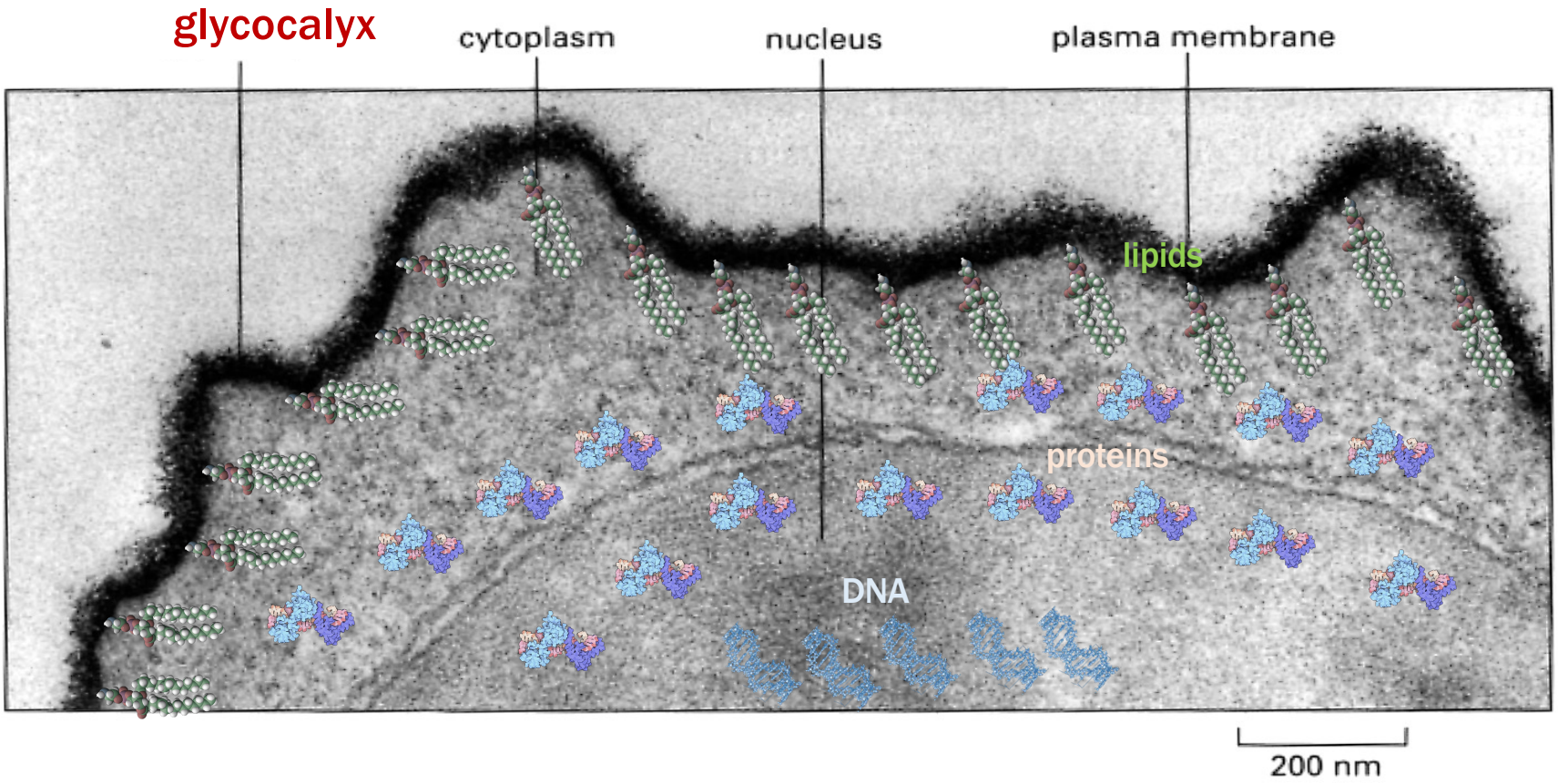


nucleic acids (DNA/RNA)

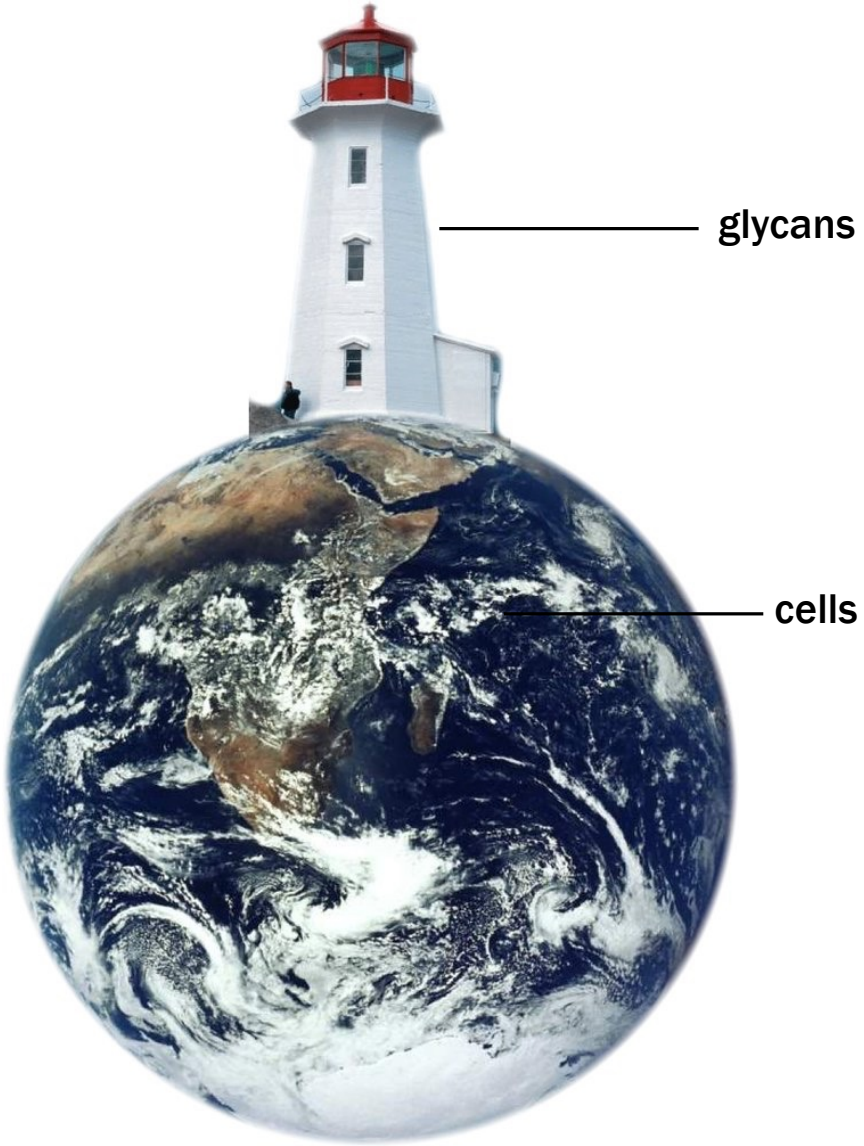


glycans (“sugars”)

glycans are predominantly located at the cell surface



as molecules located at the cell surface, glycans carry messages signaling the health and status of cells



glycans are data-rich informational molecules

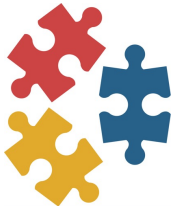
Macromolecule	Building Block	Aproximate Mass	Possible Variations in a Trimer
Protein	Amino acids	125 → 10^4-10^5	6
Nucleic Acid	Nucleotides	330 → 10^3-10^9	6
Carbohydrate	Monosaccharides	200 → 10^2-10^6	1,056 to 27,648!

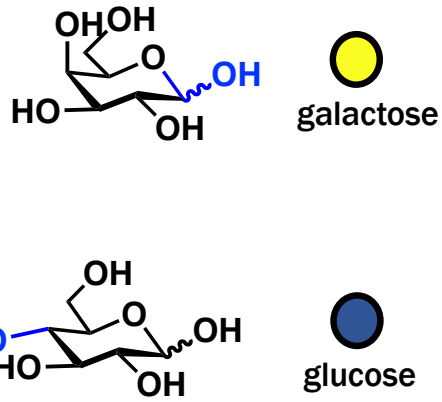
glycan building blocks are depicted as colored symbols

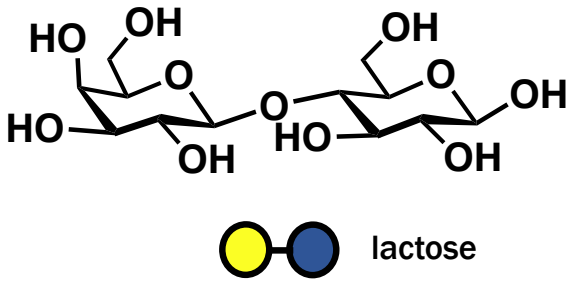
SHAPE	White (Generic)	Blue	Green	Yellow	Orange	Pink	Purple	Light Blue	Brown	Red
Filled Circle	Hexose	Glc	Man	Gal	Gul	Alt	All	Tal	Ido	
Filled Square	HexNAc	GlcNAc	ManNAc	GalNAc	GulNAc	AltNAc	AllNAc	TalNAc	IdoNAc	
Crossed Square	Hexosamine	GlcN	ManN	GalN	GulN	AltN	AllN	TalN	IdoN	
Divided Diamond	Hexuronate	GlcA	ManA	GalA	GulA	AltA	AllA	TalA	IdoA	
Filled Triangle	Deoxyhexose	Qui	Rha		6dGul	6dAlt		6dTal		Fuc
Divided Triangle	DeoxyhexNAc	QuiNAc	RhaNAc			6dAltNAc		6dTalNAc		FucNAc
Flat Rectangle	Di-deoxyhexose	Oli	Tyv		Abe	Par	Dig	Col		
Filled Star	Pentose		Ara	Lyx	Xyl	Rib				
Filled Diamond	Deoxynonulosonate		Kdn				Neu5Ac	Neu5Gc	Neu	Sia
Flat Diamond	Di-deoxynonulosonate		Pse	Leg		Aci		4eLeg		
Flat Hexagon	Unknown	Bac	LDmanHep	Kdo	Dha	DDmanHep	MurNAc	MurNGc	Mur	
Pentagon	Assigned	Api	Fru	Tag	Sor	Psi				

https://www.ncbi.nlm.nih.gov/glycans/snfg.html

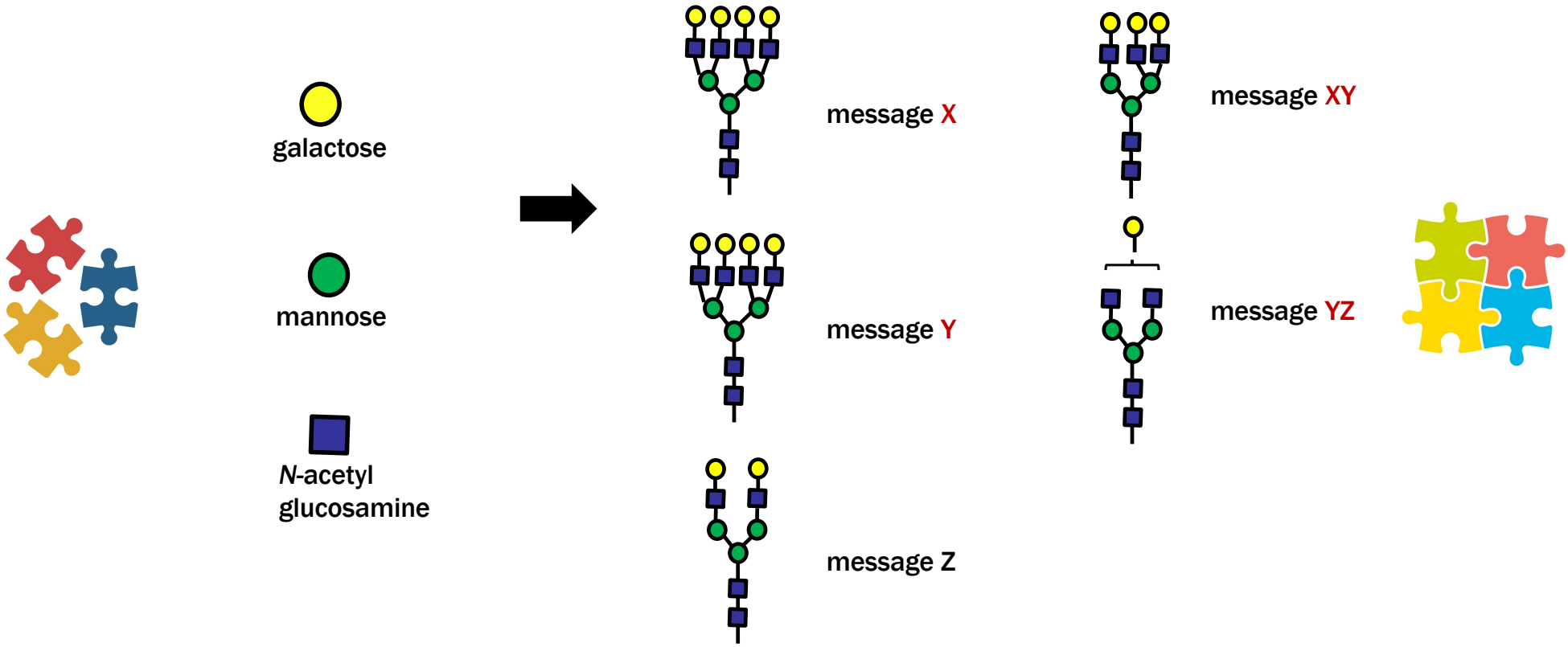
glycan building blocks are assembled into other glycans with different messages



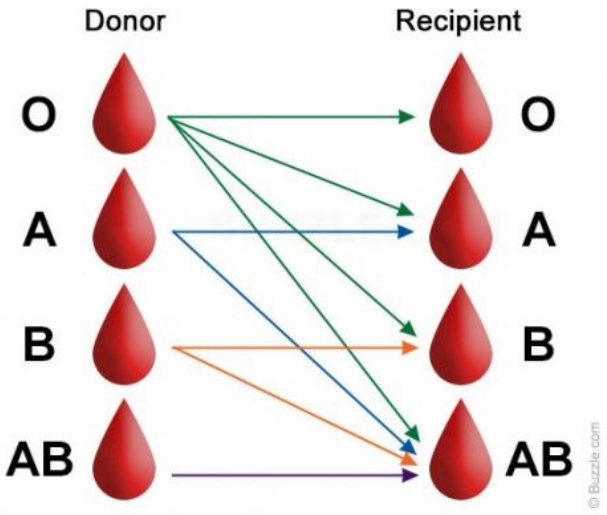




glycan building blocks are assembled into other glycans with different messages



cell surface glycans dictate blood compatibility

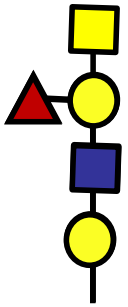


	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in Plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in Red Blood Cell	A antigen	B antigen	A and B antigens	None

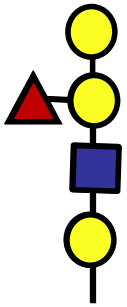
InvictaHOG/Wikimedia Commons/Public Domain Image

cell surface glycans dictate blood compatibility

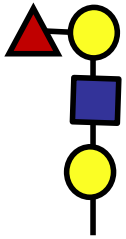
group A



group B

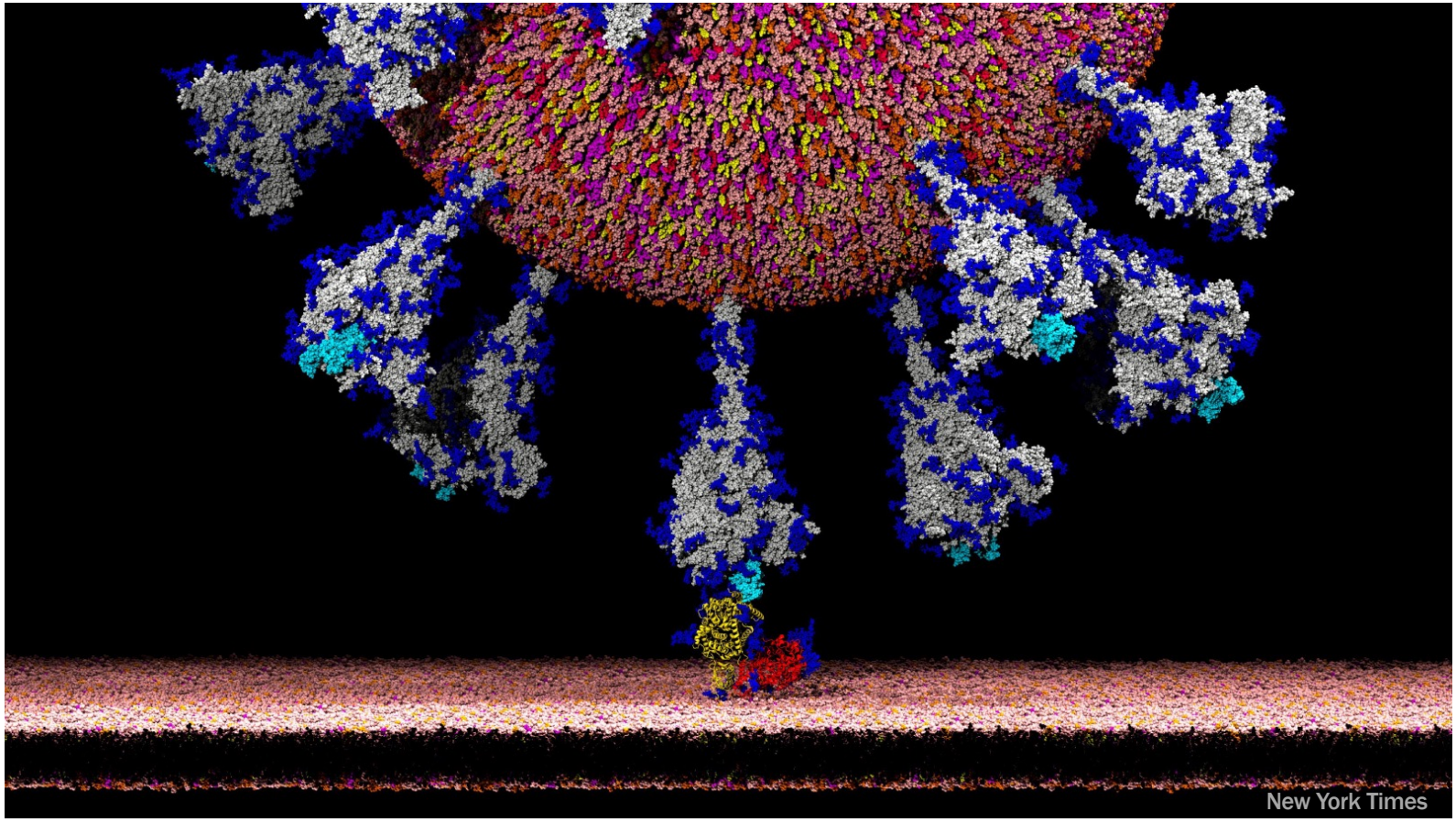


group O

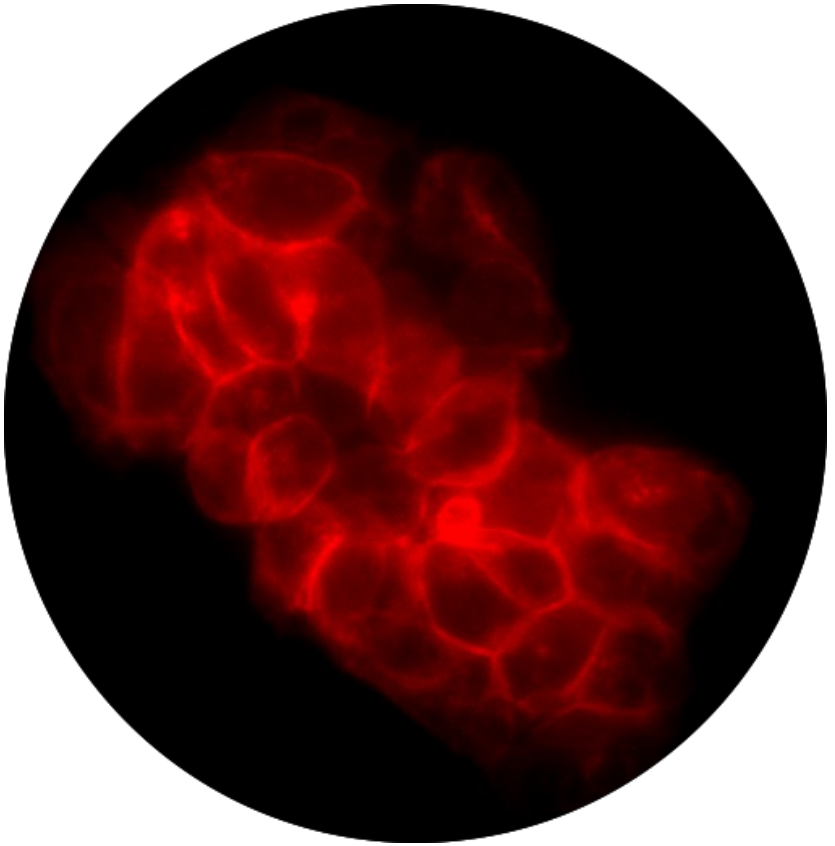


InvictaHOG/Wikimedia Commons/Public Domain Image

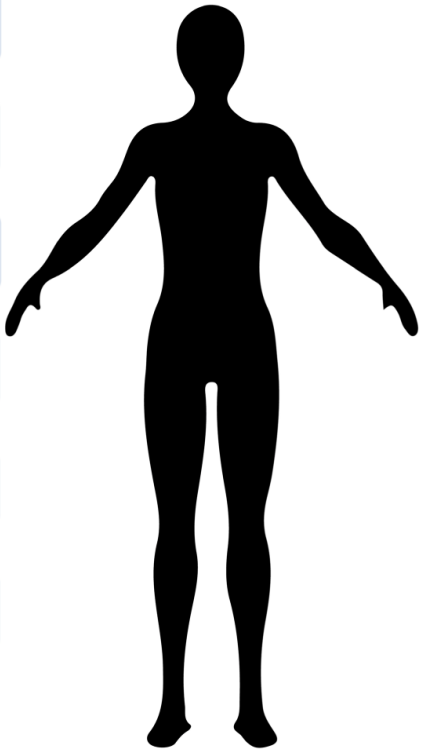
viruses are also coated with glycans!



“Ok, so they are everywhere, but does it mean they are important?”



errors in the cellular production or removal of glycans lead to congenital disorders of glycosylation

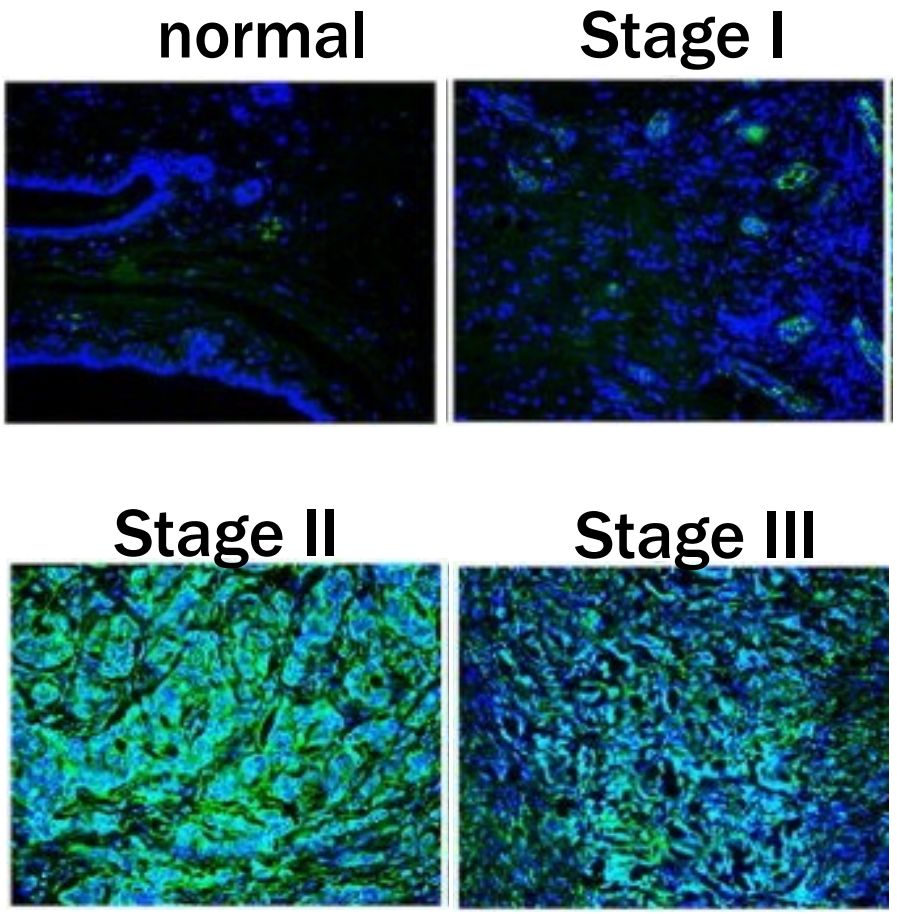


Cleft palate VSD	Congenital malformations	Neurologic involvement	Developmental delay Seizures Stroke-like episodes Peripheral neuropathy Cerebellar ataxia Hypotonia
Strabismus Retinitis pigmentosa Cataract	Ophthalmologic involvement		
Growth failure Hyperthyroidism Hypoglycemia Hypogonadism	Endocrine involvement	Cardiac involvement	Pericarditis Cardiomyopathy Structural heart defects
	Muscle involvement	Gastrointestinal involvement	Failure to thrive Vomiting Diarrhea Protein-losing enteropathy
Hepatopathy Hepatomegaly Cholestasis Liver failure	Hepatic involvement	Renal involvement	Kidney cysts Nephrotic syndrome Dysplastic kidneys
Hypocholesterolemia Hypercholesterolemia	Lipid abnormalities	Hematologic involvement	Thrombosis Bleeding Anemia
Recurrent infections	Infections and immune involvement	Skeletal involvement	Kyphoscoliosis Skeletal dysplasia Osteopenia

Verheijen (2019) ***Genetics in Medicine***

errors in the cellular production or removal of glycans lead to congenital disorders of glycosylation

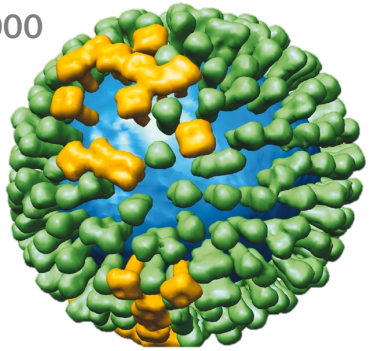
changes in glycan abundance and composition accompany cancers and their progression

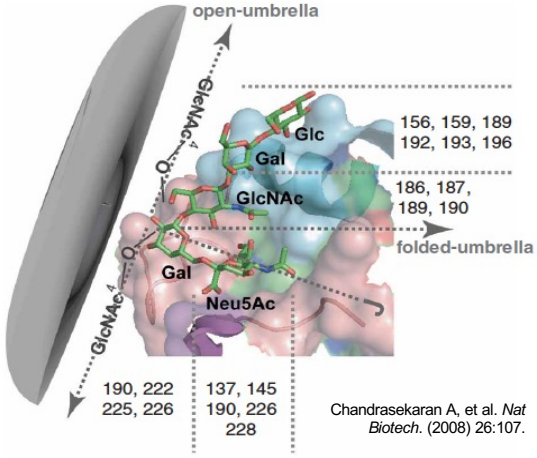


Gill (2016) *Histochemistry & Cell Biology*

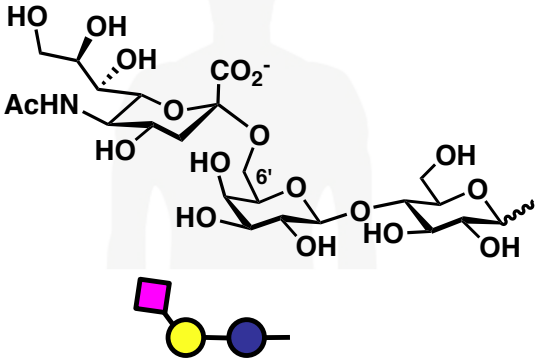
viruses can evolve to recognize human glycans for infection

Hemagglutinin (HA)
300-1000 copies

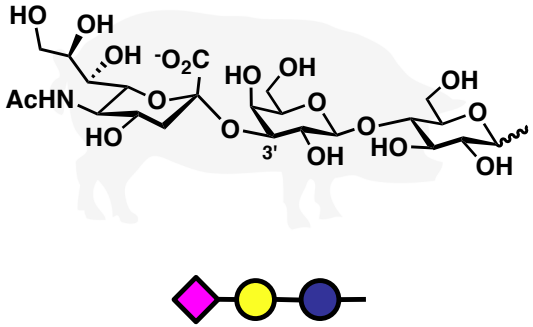




Chandrasekaran A, et al. *Nat Biotech.* (2008) 26:107.



(α2-6) 6′-sialyllactose



(α2-3) 3′-sialyllactose

NOBELPRISET I KEMI 2022
THE NOBEL PRIZE IN CHEMISTRY 2022

KUNGL. VETENSKAPS-AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES


Photo: Grace Science Foundation

Carolyn R. Bertozzi
Stanford University
USA


Photo: University of Copenhagen

Morten Meldal
University of Copenhagen
Denmark

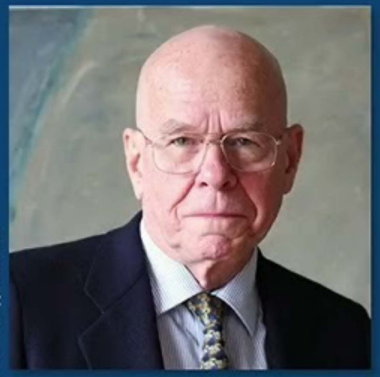


Photo: Scripps Research

K. Barry Sharpless
Scripps Research
USA

”för utveckling av klickkemi och bioortogonal kemi”

“for the development of click chemistry and bioorthogonal chemistry”

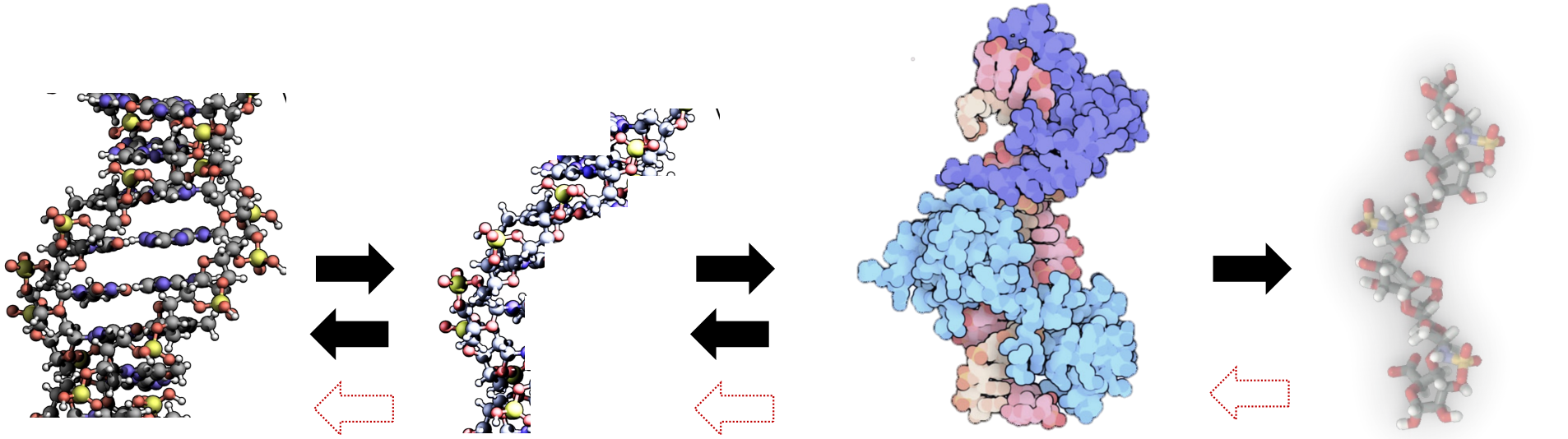
#nobelprize

THE NOBEL PRIZE

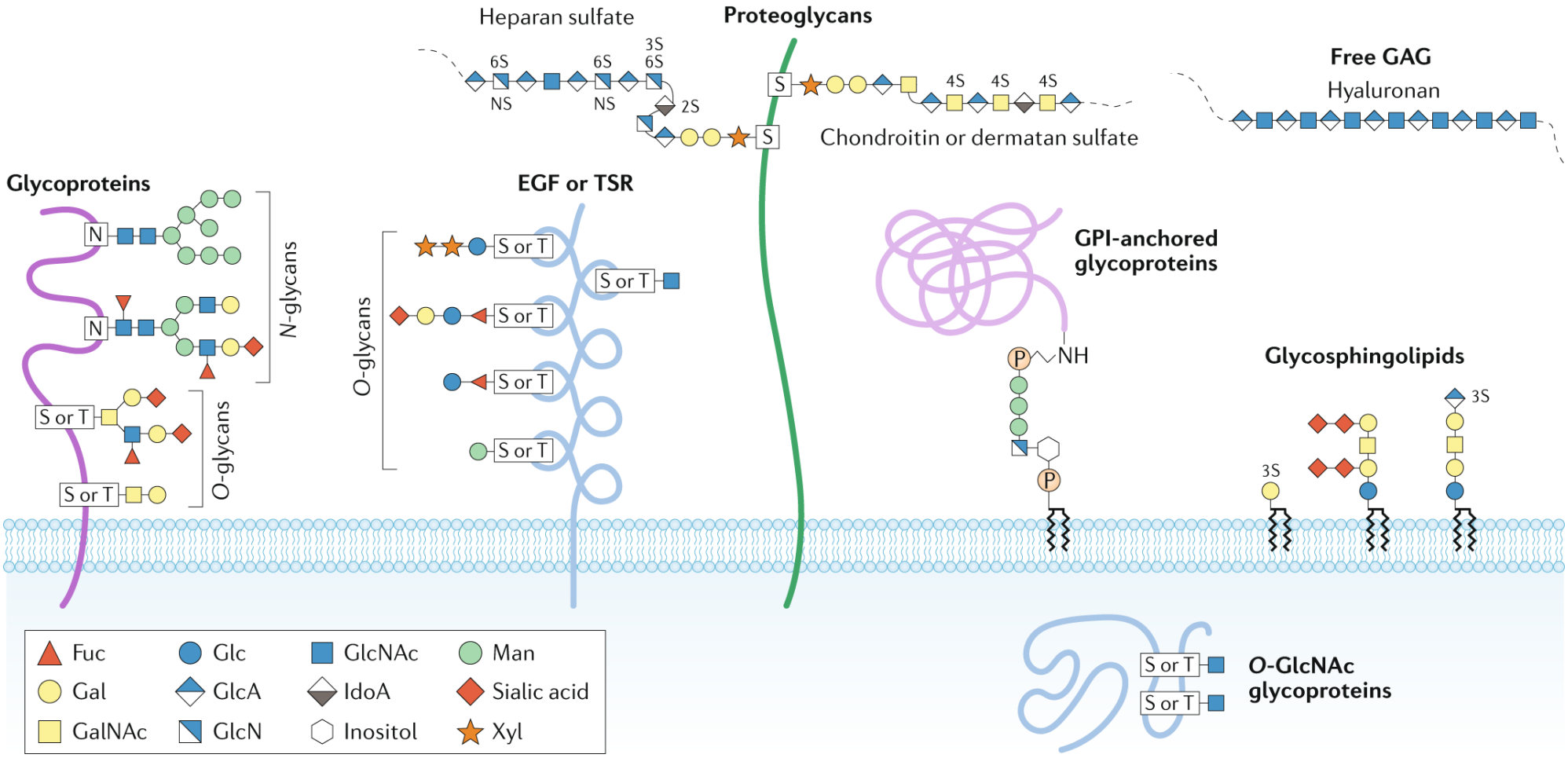
“Ok, so glycans are everywhere, and they seem to be changing in health and disease.

How come we haven’t heard about them before?”

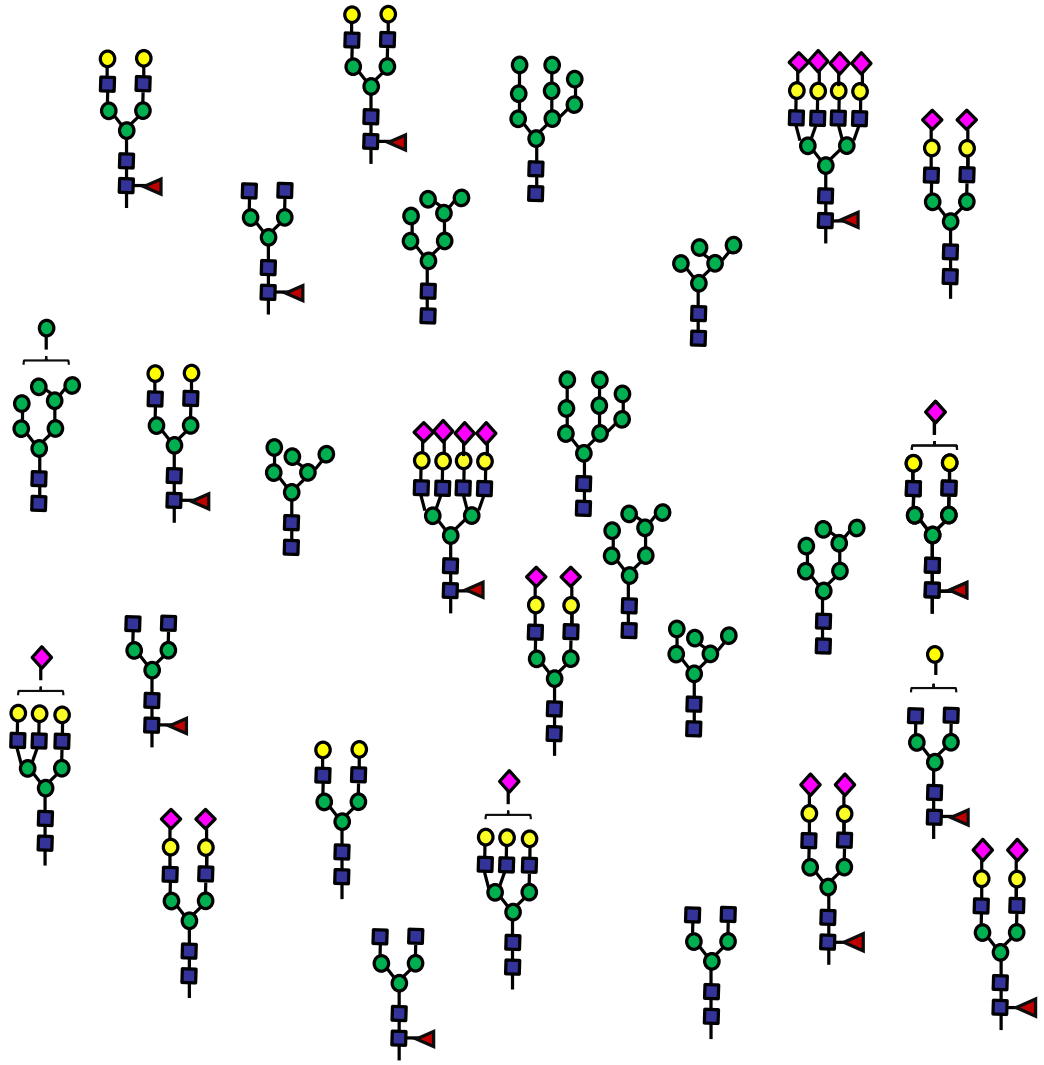
glycan abundance and composition are difficult to predict from the central dogma



there is extreme informational complexity in glycans



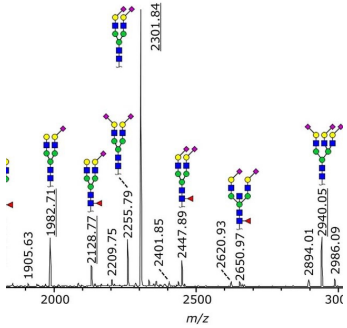
we appreciate
complexity



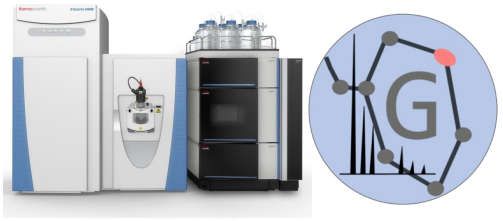
we appreciate complexity

when equipped with the right tools, training, and environment

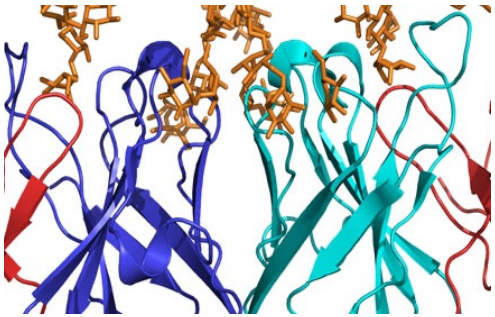
analytics



state of the art instrumentation & bioinformatics



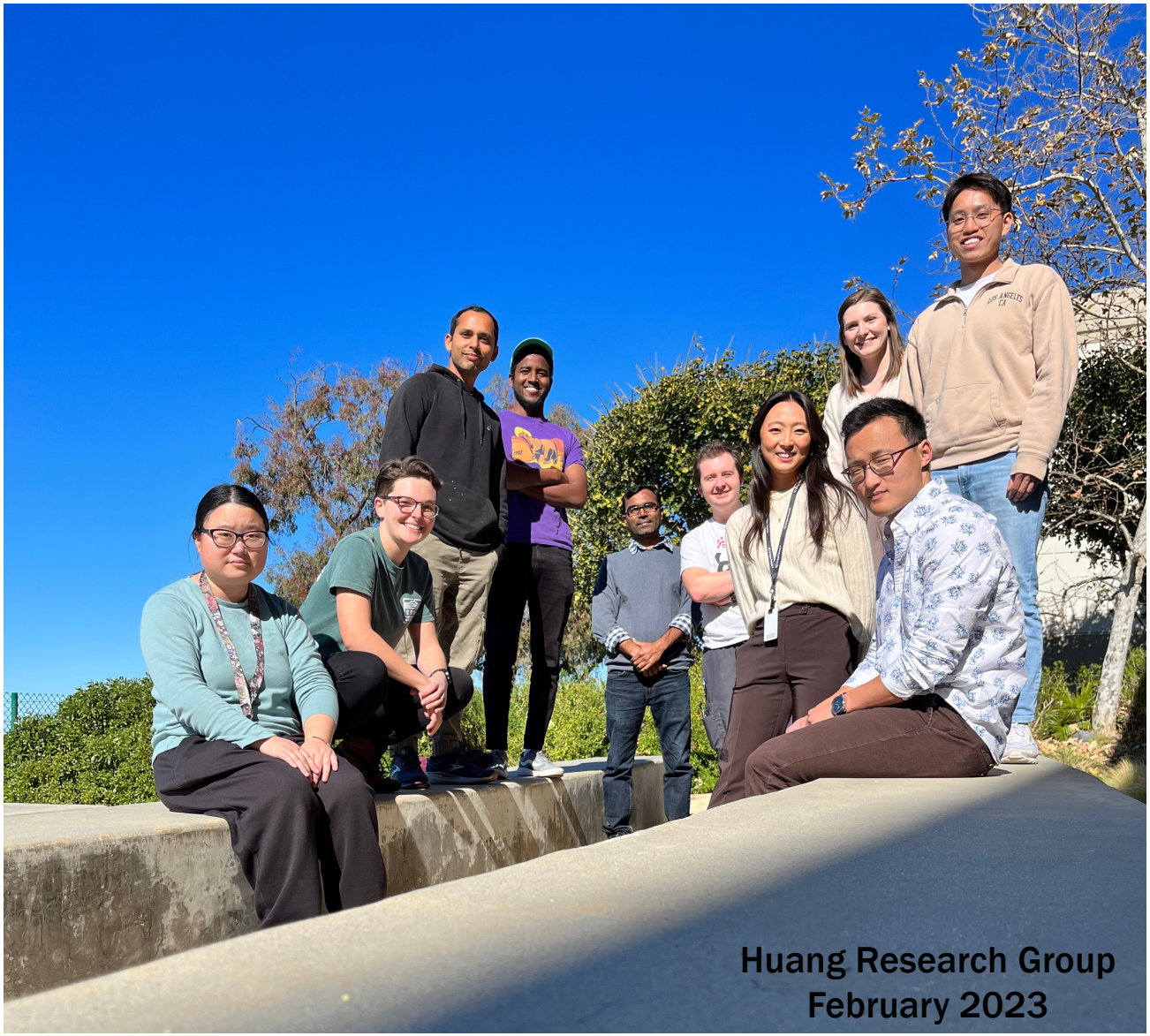
chemical glycobiology



chemical expertise

we appreciate complexity

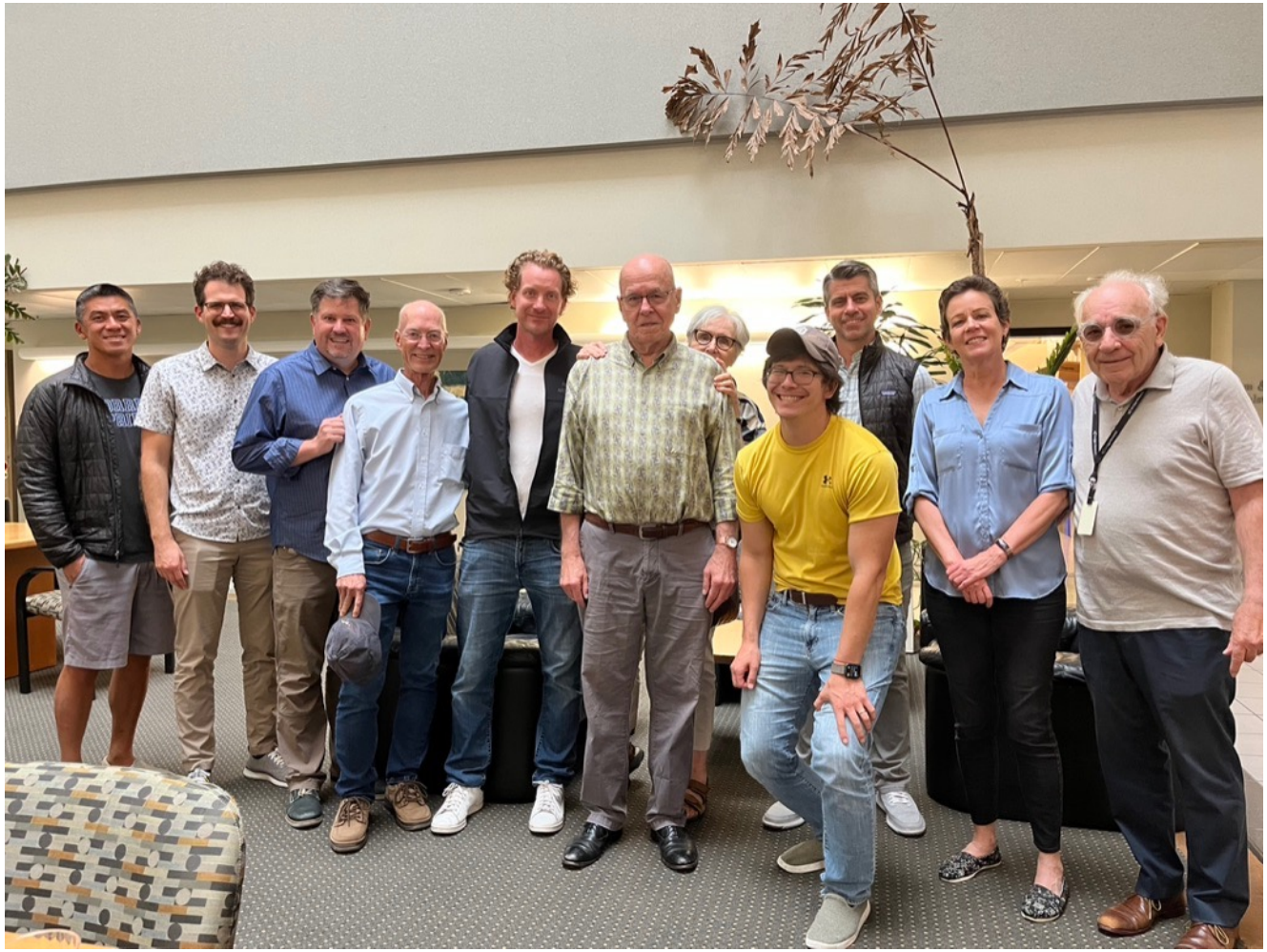
when equipped with the right tools, training, and environment



we appreciate complexity

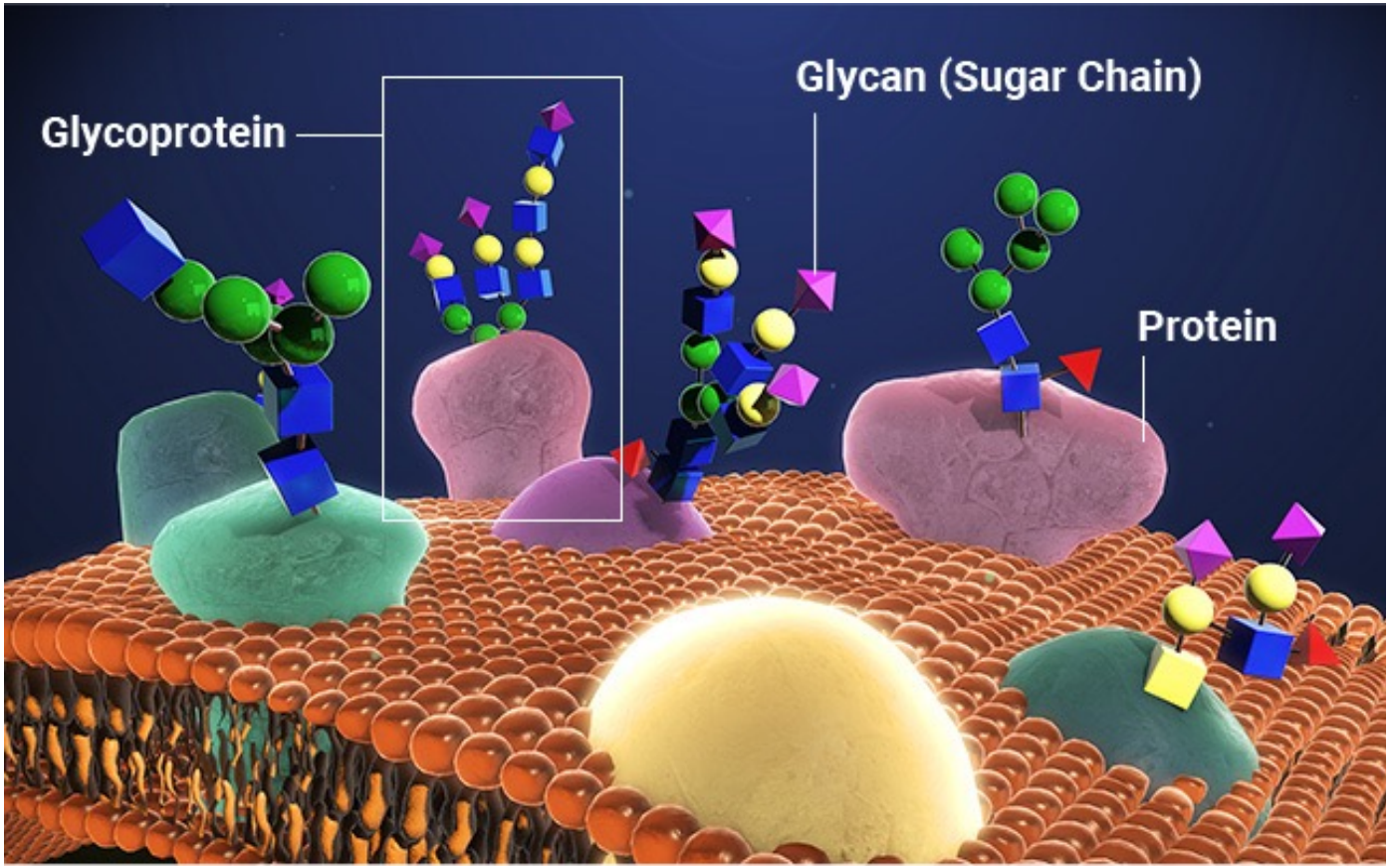
when equipped with the right tools, training, and environment

Sharpless Nobel Prize in Chemistry Announcement | October 2022



our strategy

connecting proteins with glycans

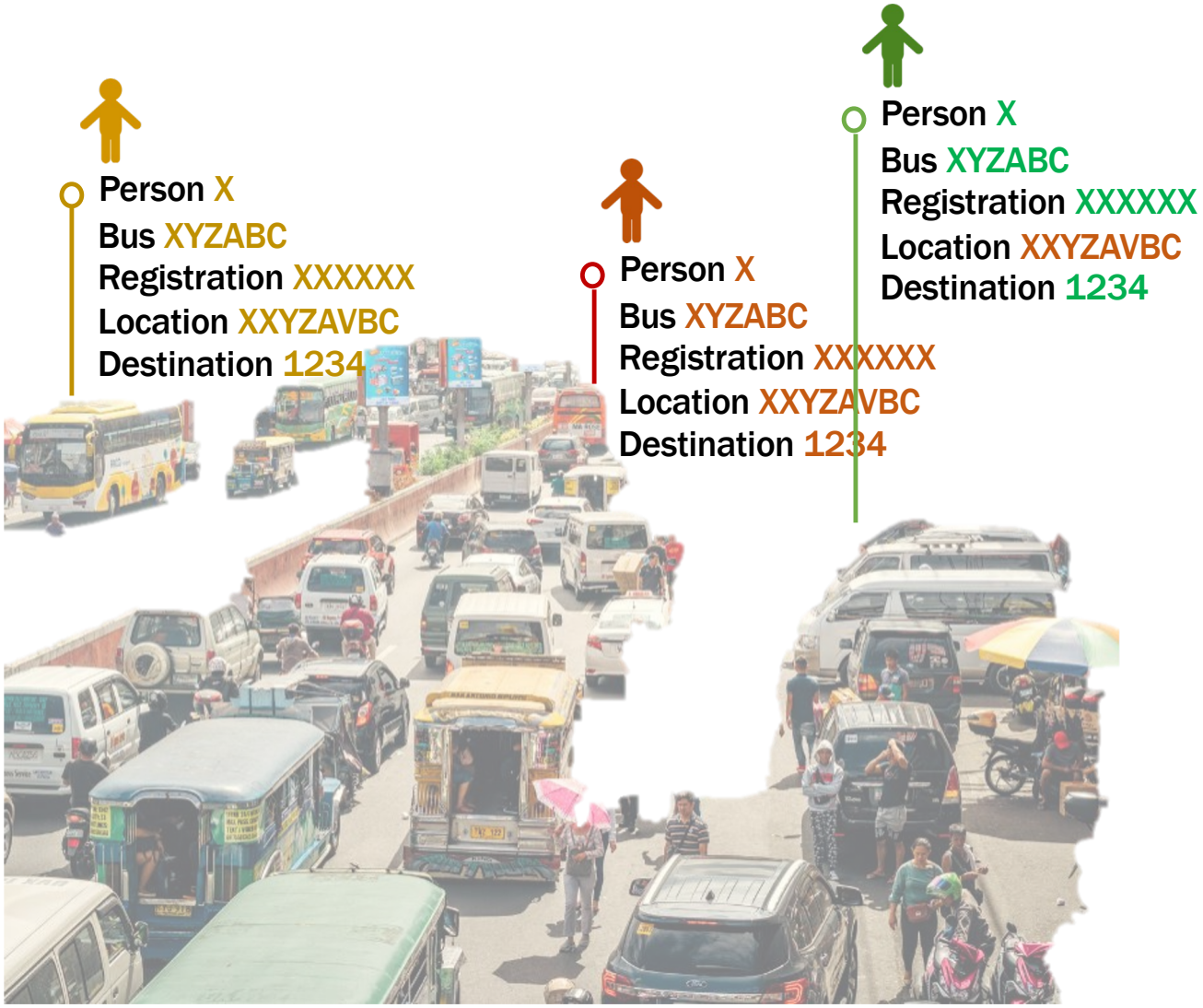


our strategy

connecting proteins with glycans

our strategy

connecting proteins with glycans



1

discover changes in protein glycosylation

2

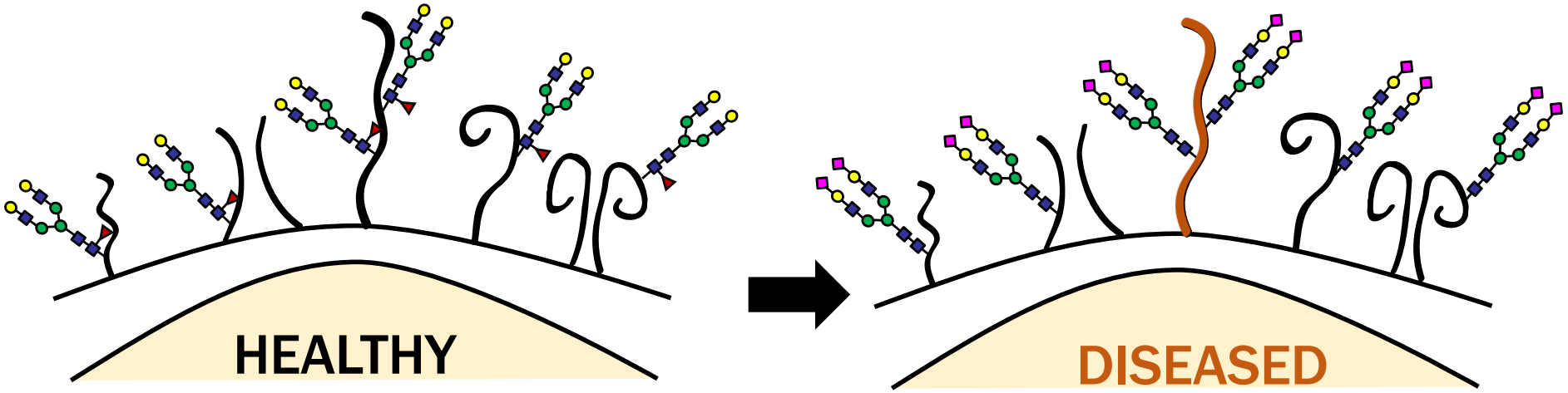
define how & why protein glycosylation is changing

3

exploit change in protein glycosylation → detection therapeutics

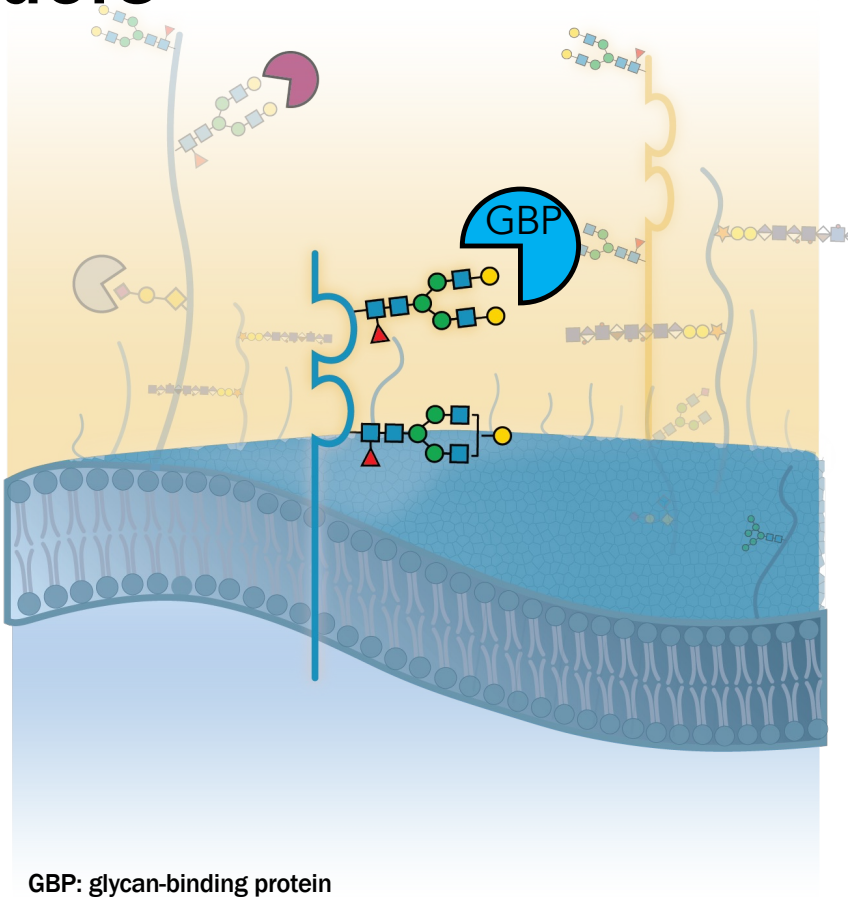
1

discover changes in protein glycosylation



1

use glycan-binding proteins as message decoders

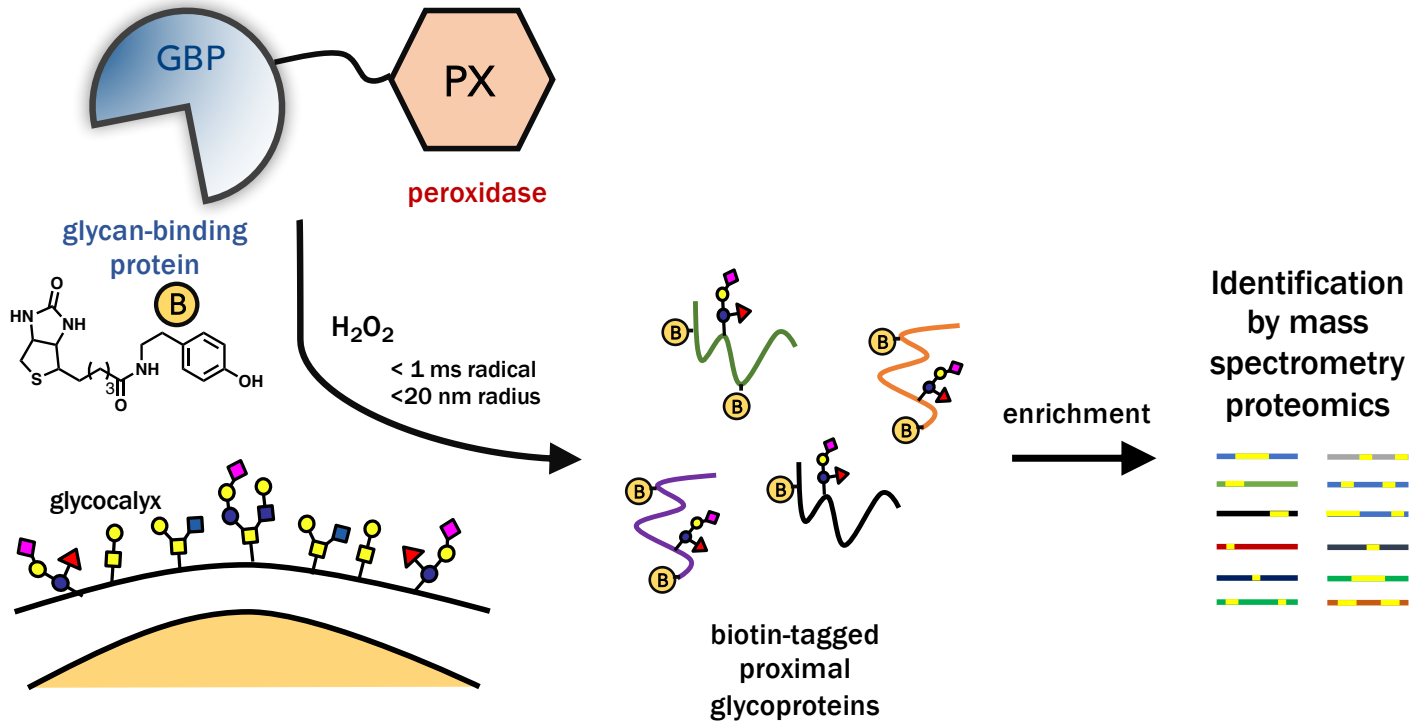


GBP: glycan-binding protein

1

discover protein glycosylation changes using GBPs as decoders

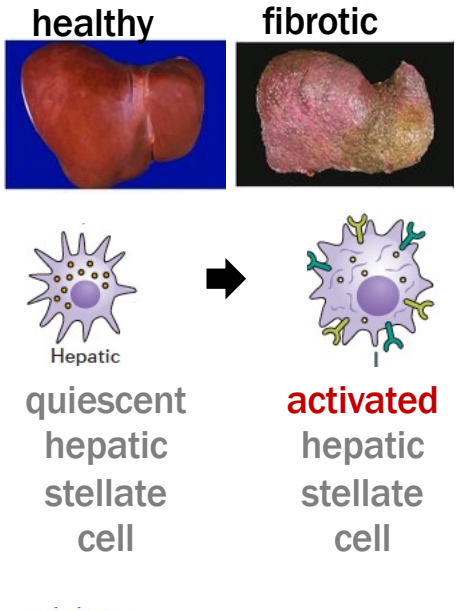
IN SITU PROXIMITY TAGGING



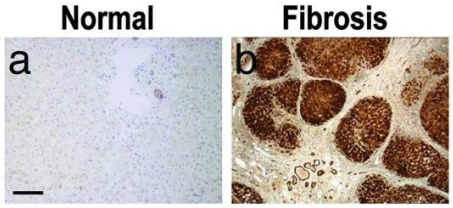
Joeh et al., Mapping glycan-mediated galectin-3 interactions by live cell proximity labeling. *PNAS* (2020) 117:27329.

1

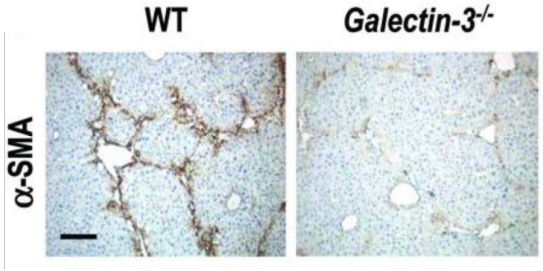
galectin-3 is a glycan-binding protein necessary in hepatic fibrosis



upregulated in liver fibrosis



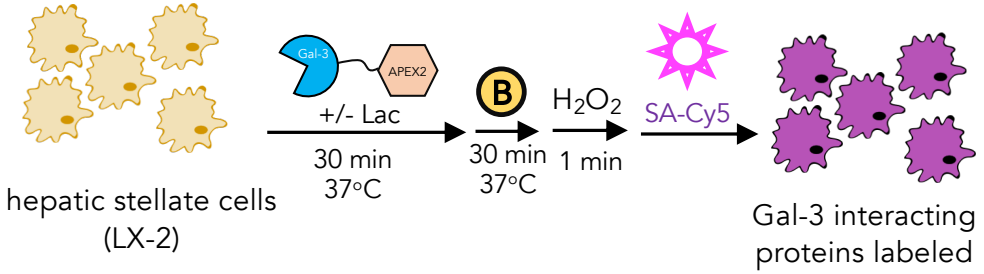
Gal3$^{-/-}$ mice exhibit reduced fibrosis

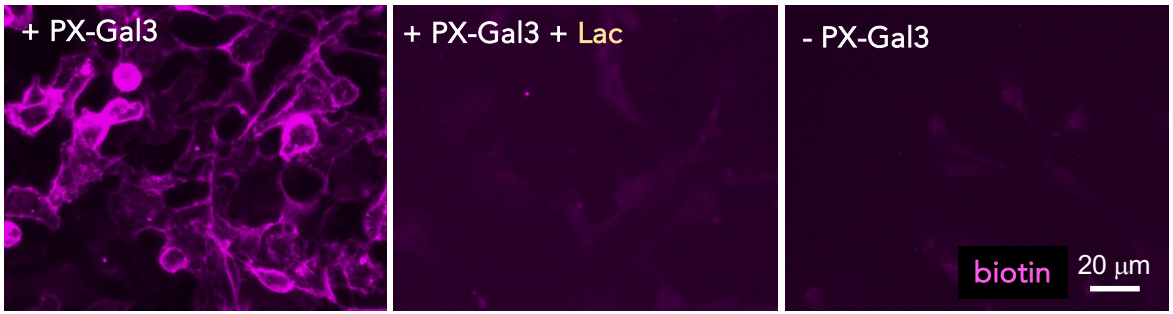


Henderson NC, et al. *PNAS* (2006) 103:5060.
Iredale. *J Clin Invest* (2007) 117:539.
Battaler, Brenner. J Clin Invest (2005) 115:209
Tsuchida T, Friedman SL. *Nat Rev* (2017) 14:397.

1

proximity labeling of live hepatic stellate cells

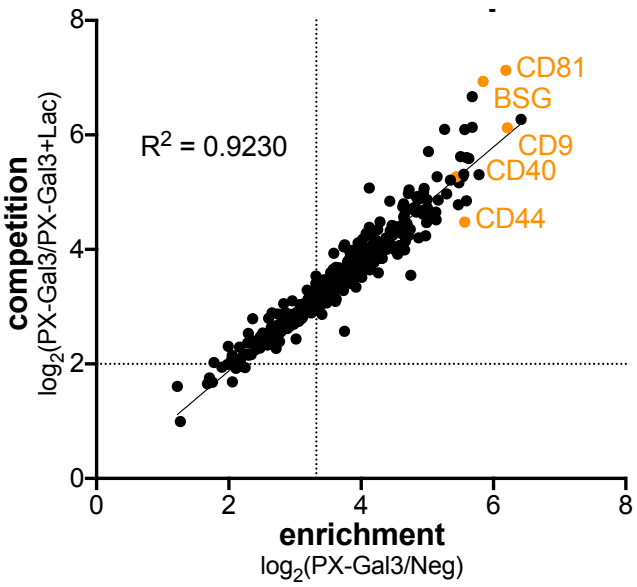


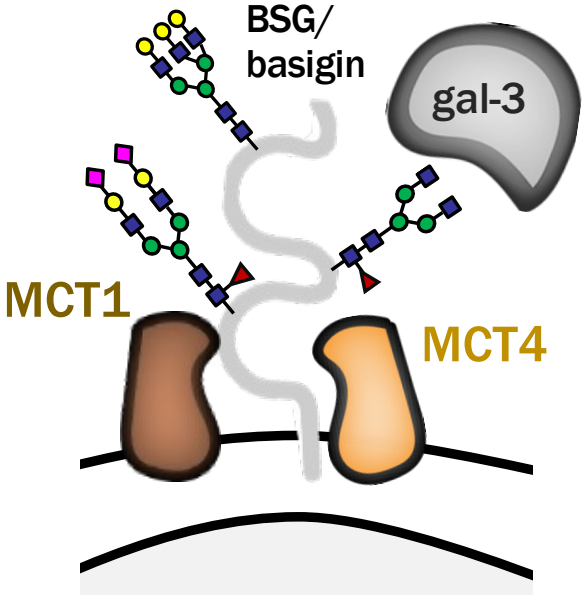


Joeh et al., Mapping glycan-mediated galectin-3 interactions by live cell proximity labeling. *PNAS* (2020) 117:27329.

1

discovery of basigin glycoprotein as a messenger for galectin-3





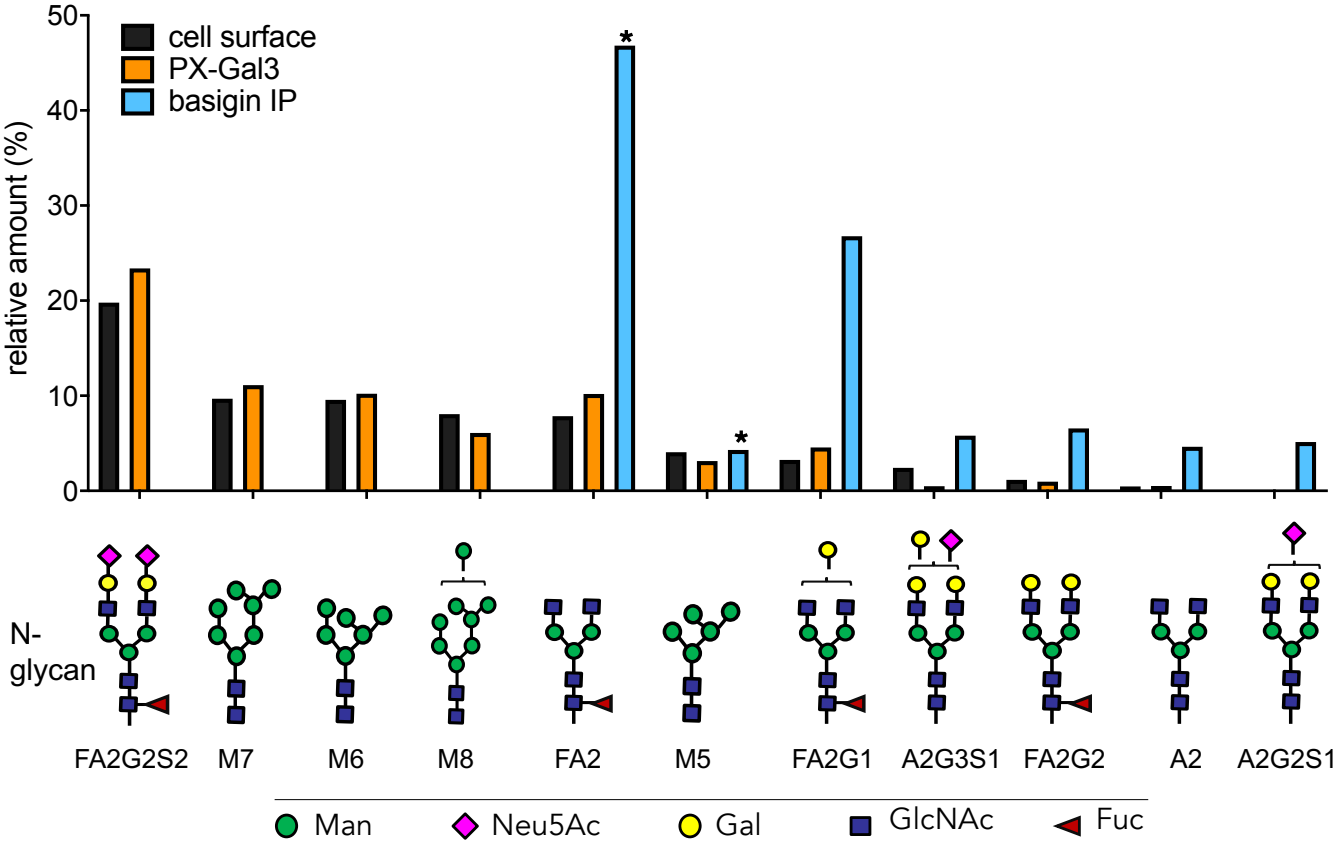
Joeh et al., Mapping glycan-mediated galectin-3 interactions by live cell proximity labeling. *PNAS* (2020) 117:27329.

2

define how & why protein glycosylation is changing

2

glycomics mass spectrometry reveals glycan patterns

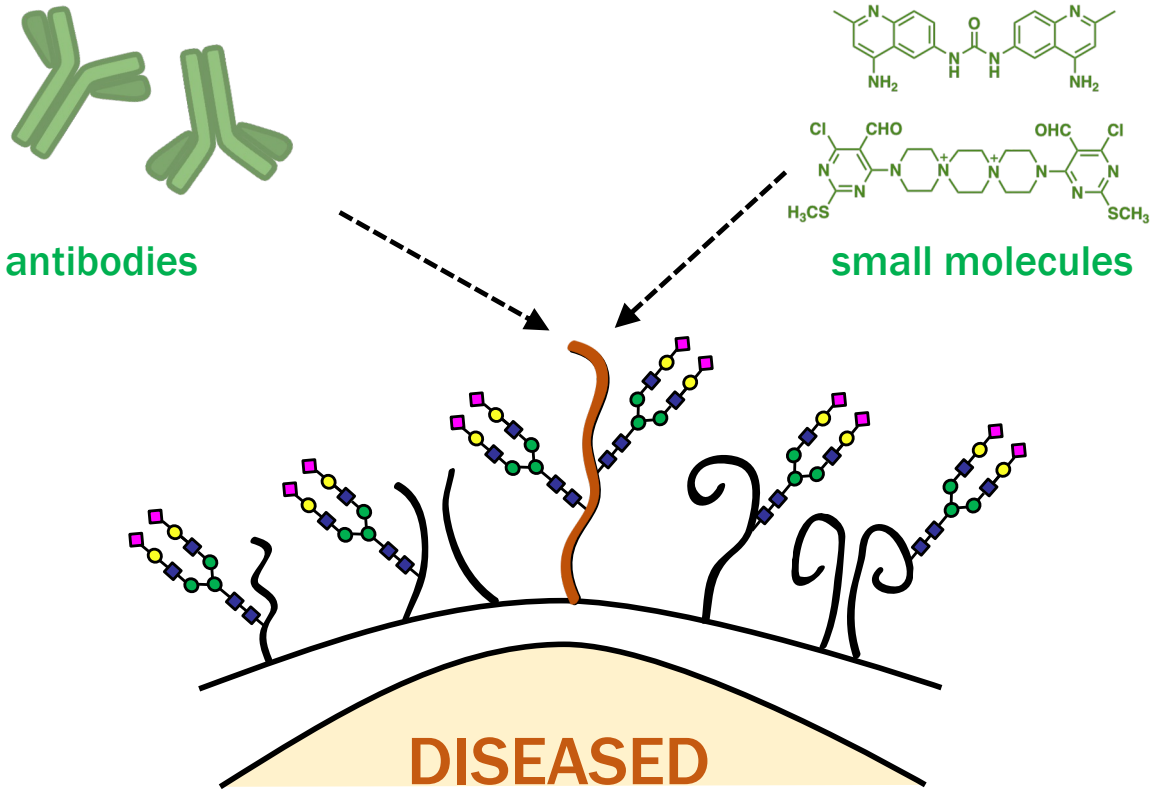


3

exploit change in protein glycosylation

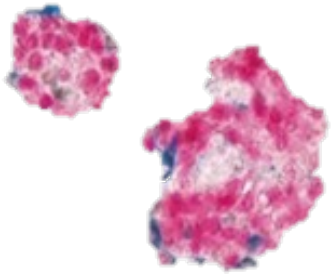
3

antibodies and small molecules expedite detection and targeting



cancers are

lethal



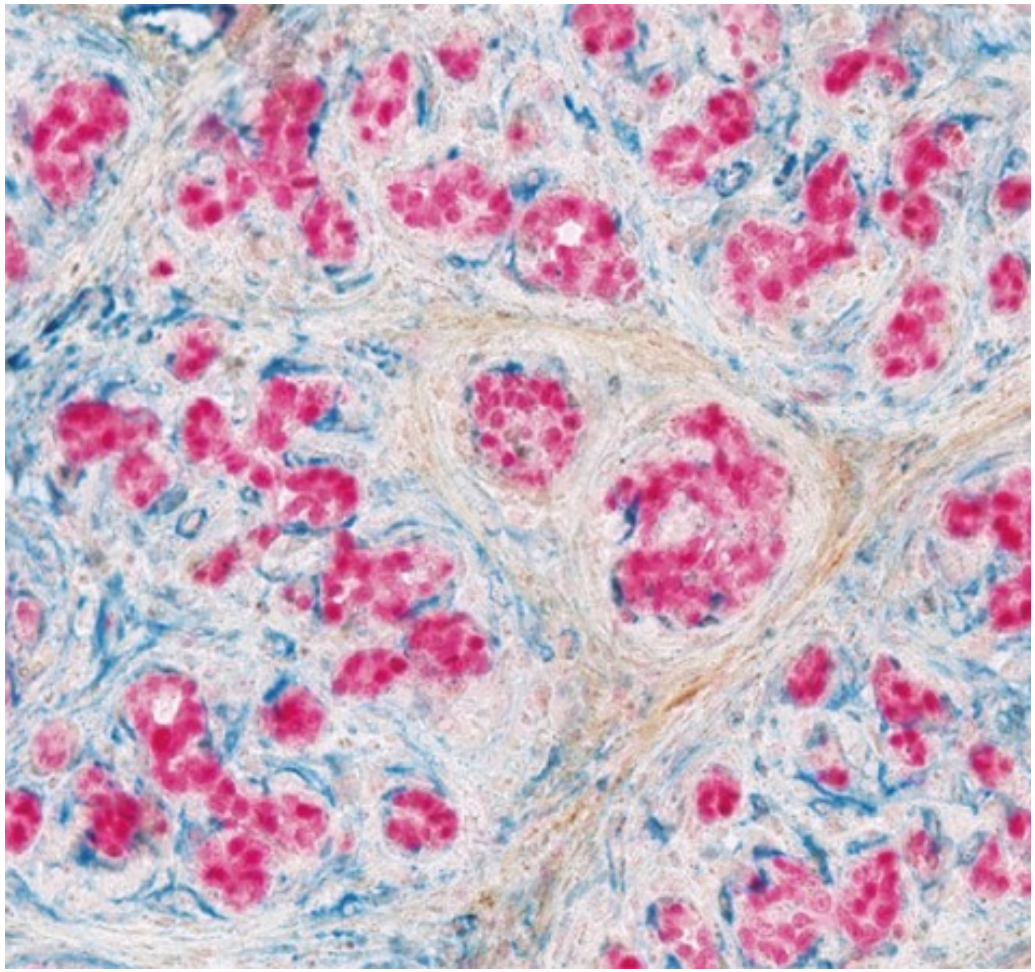
3

pancreatic ductal adenocarcinoma (PDAC)

Hosein (2020) *Nat Rev Gastroenterol Hepatol*

stromal cancers are lethal and are not efficiently served by current therapies

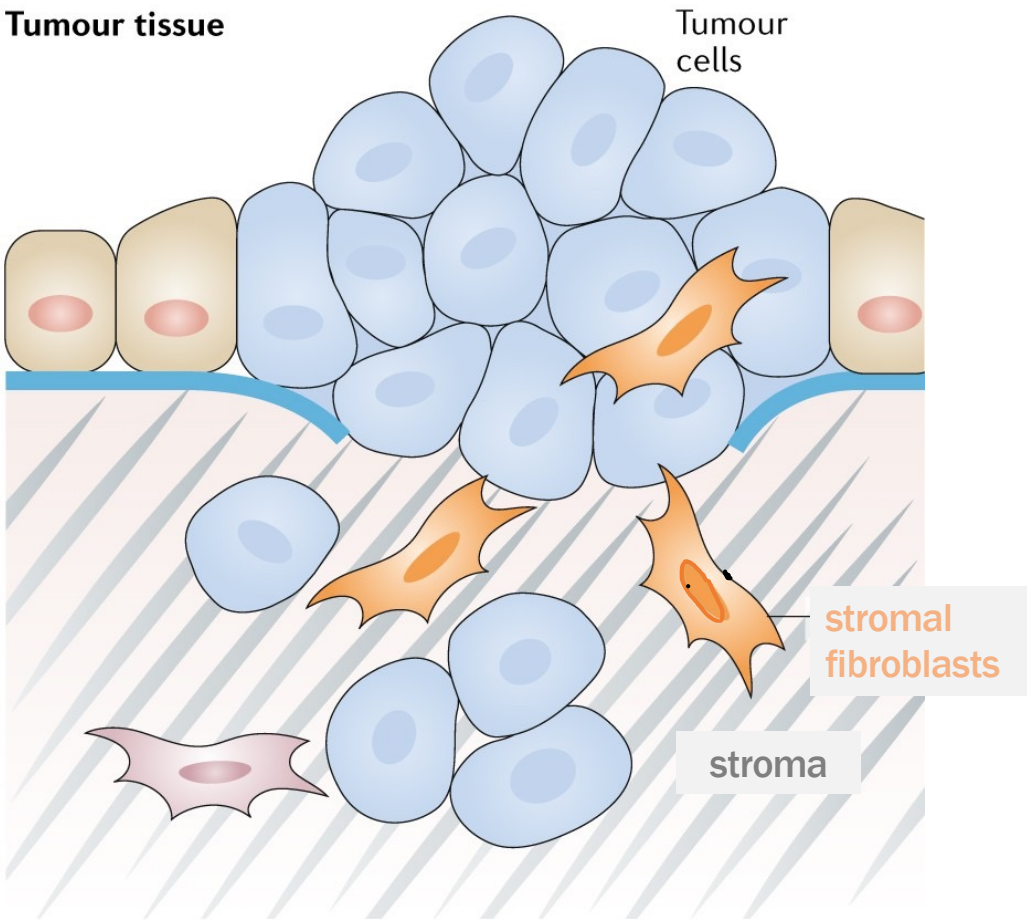
3



pancreatic ductal adenocarcinoma (PDAC)

most anticancer therapies target only cancer cells, but the tumor stroma promotes resistance to these therapies

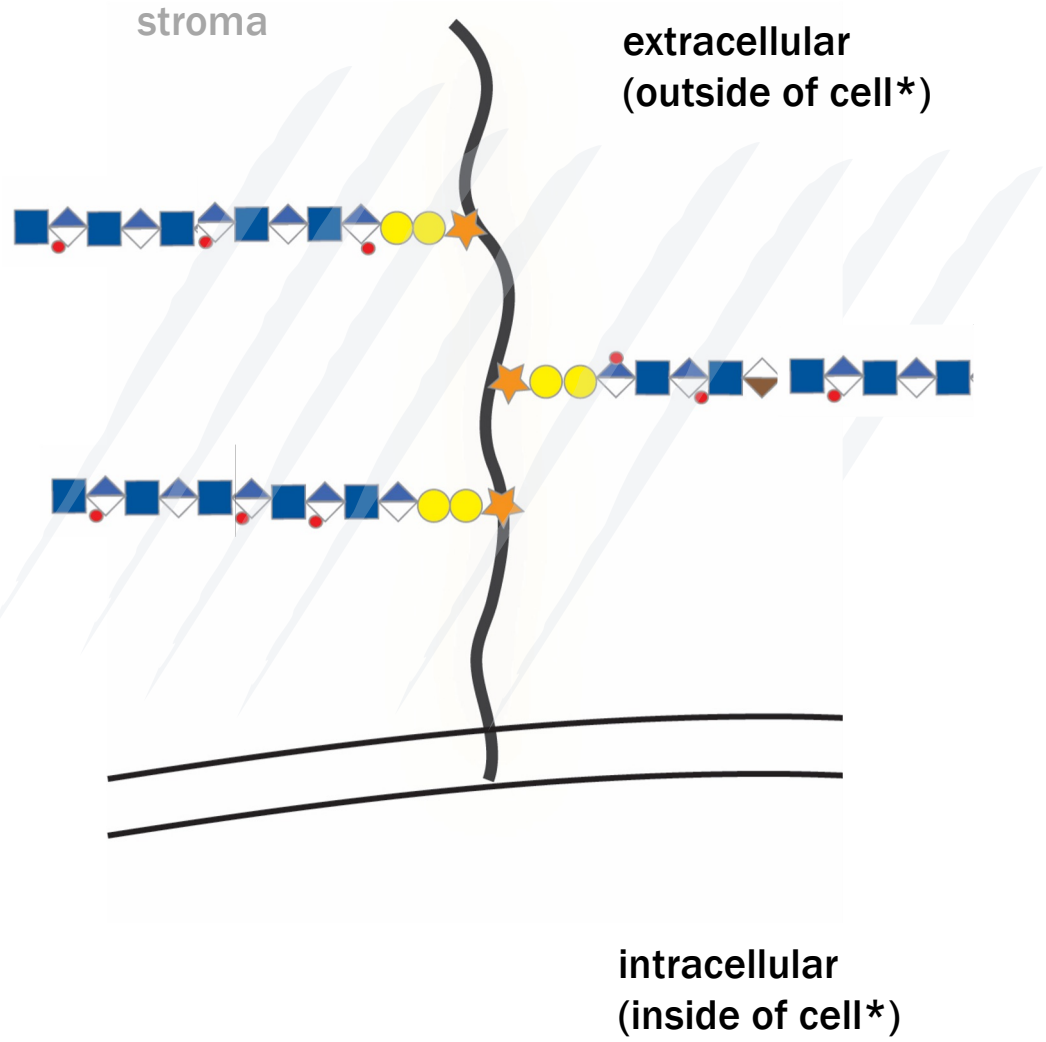
3



Valkenburg (2018) *Nat Rev Clinical Oncology*

proteoglycans in the stroma shield tumors from attack and create signals that tells cancer cells to grow excessively

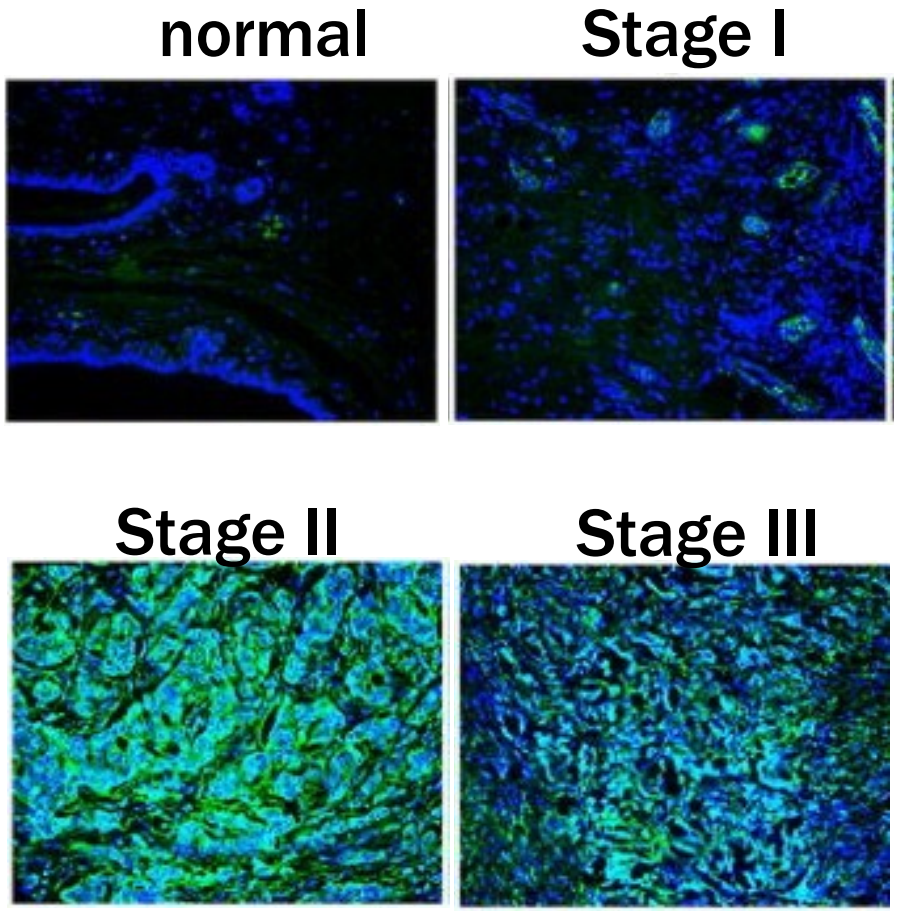
3



*tumor and fibroblast cells

proteoglycans are pathogenically abundant in metastasic cancers

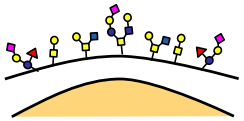
3



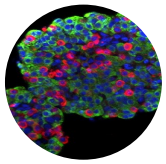
Gill (2016) *Histochemistry & Cell Biology*

Cancer tissue types: pancreatic ductal adenocarcinoma (PDAC): Draetta *Nature 2018* | Triple Negative Breast Cancer | Multiple Myeloma (Rapraeger, Sanderson) | Prostate Cancer

SUMMARY

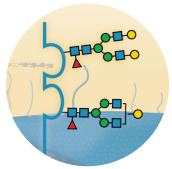


Glycans are a fascinating set of informational biomolecules

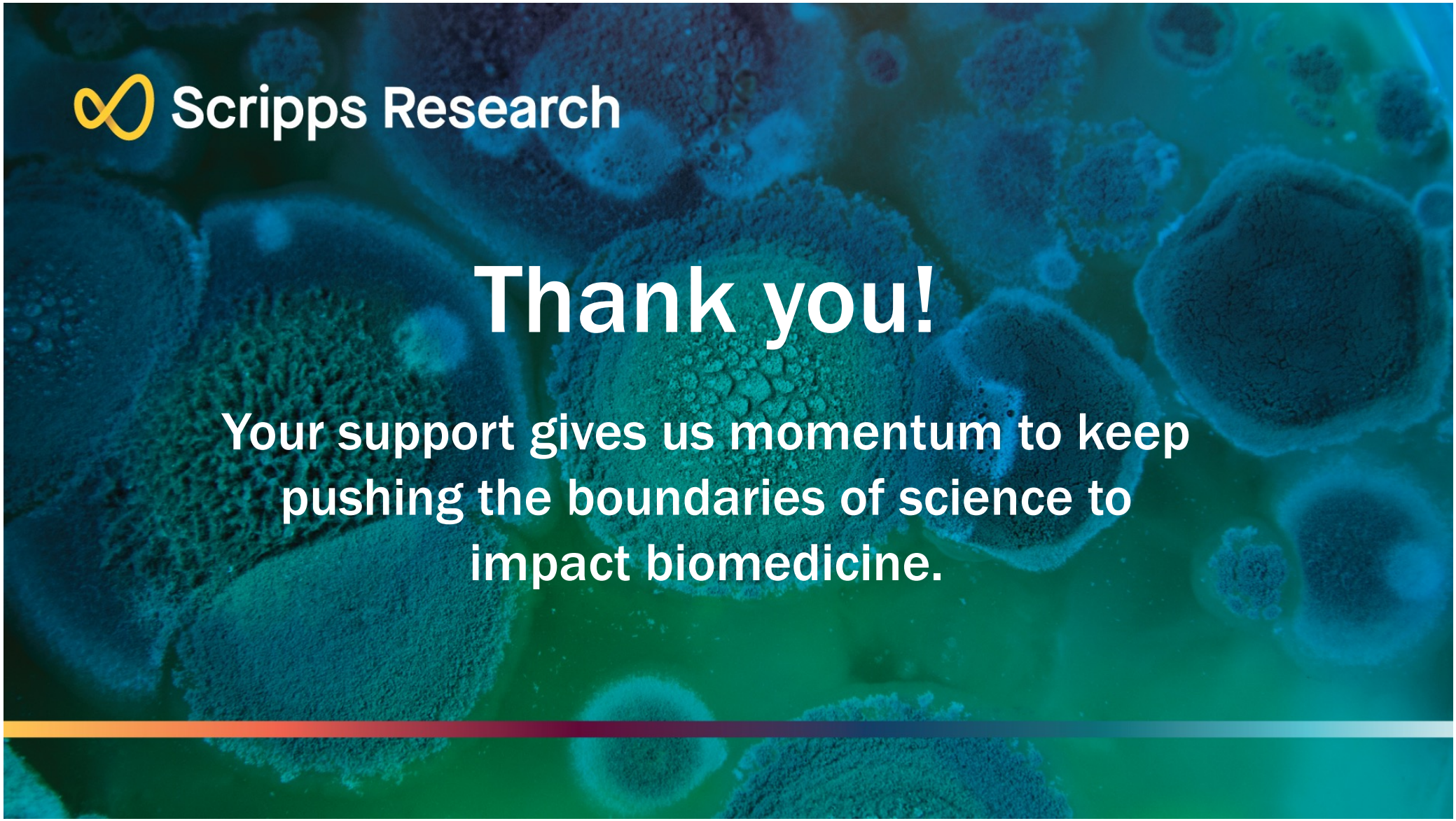


Glycan patterns are changed in disease

Detection of changes in glycan patterns requires invention of techniques



Studying protein glycosylation may enable precision diagnostics and therapeutic avenues


Scripps Research
Thank you!
Your support gives us momentum to keep pushing the boundaries of science to impact biomedicine.