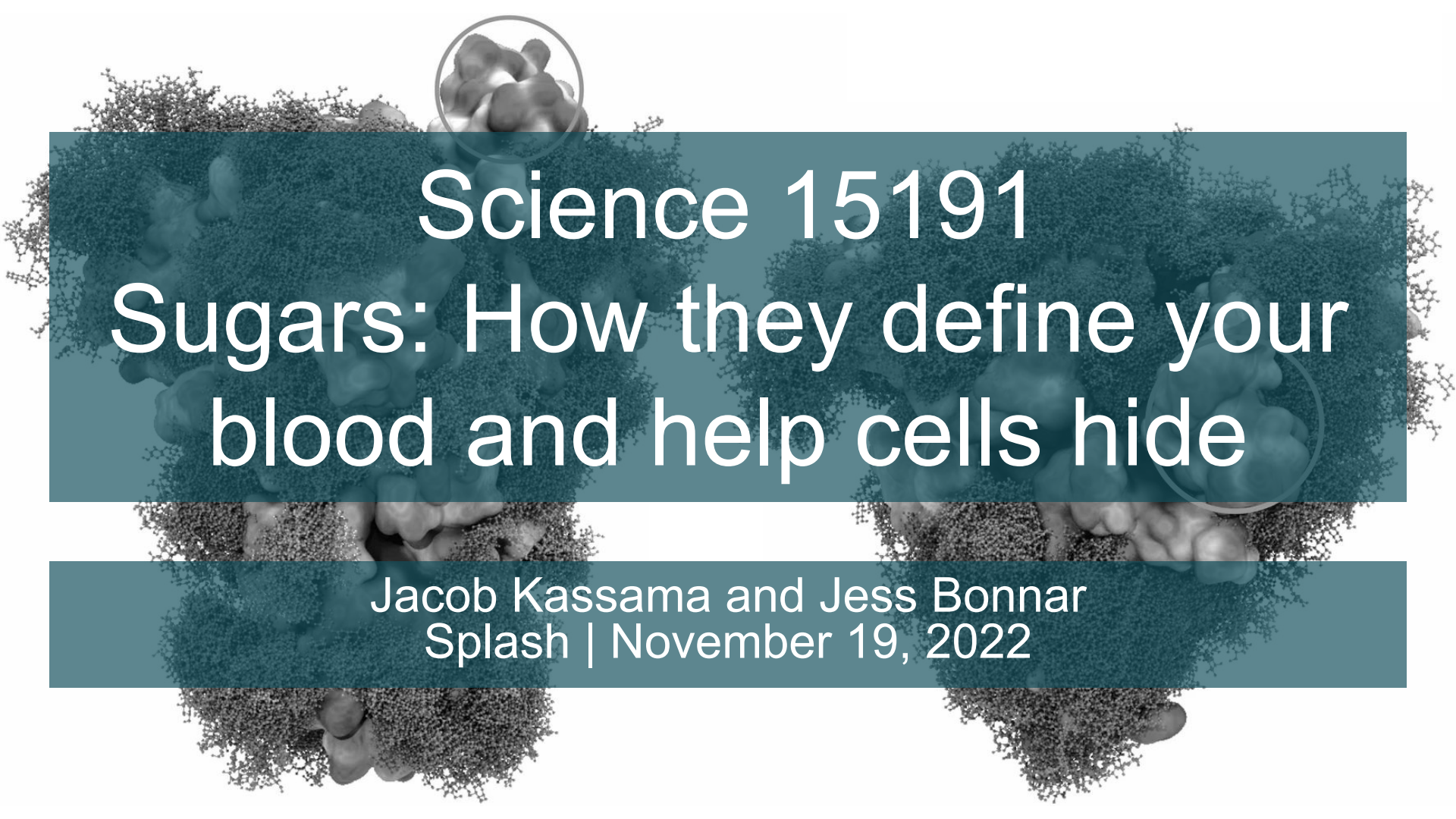


Science 15191
Sugars: How they define your blood and help cells hide

Jacob Kassama and Jess Bonnar
Splash | November 19, 2022

We are PhD students in the MIT Biology department!

Jacob | he/him/his | Hometown: Huntsville, AL

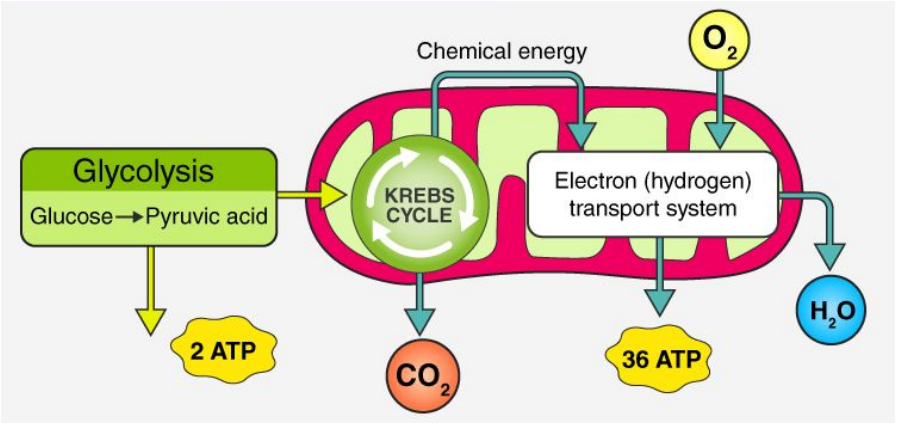
Previous research: how bacterial cell surface sugar structures help them evade the immune system

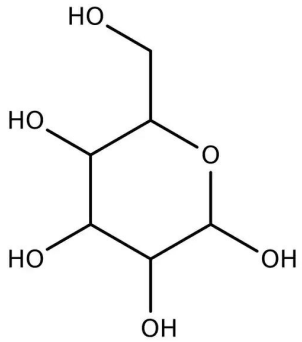
Jess | she/her/hers | Hometown: Visalia, CA

Previous research: how the cell folds membrane proteins and how we can build CRISPR-based tools to find new biology

Food!

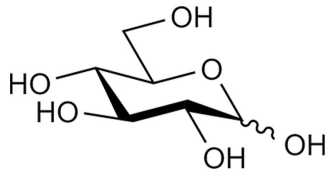
Cellular Respiration





$C_6H_{12}O_6$

Glucose



byjus.com/biology/cellular-respiration/

Electron micrograph, brush border of intestine
cellimagelibrary.org/images/10929

Every cell on earth has a sugar coat!

1. How do these sugar coats get made?
2. What do these sugar coats do?
    - Blood type
    - Cancer cell evasion
    - Many other important things we won't discuss today!

Glycosylation

Glyco – Greek prefix for sugar

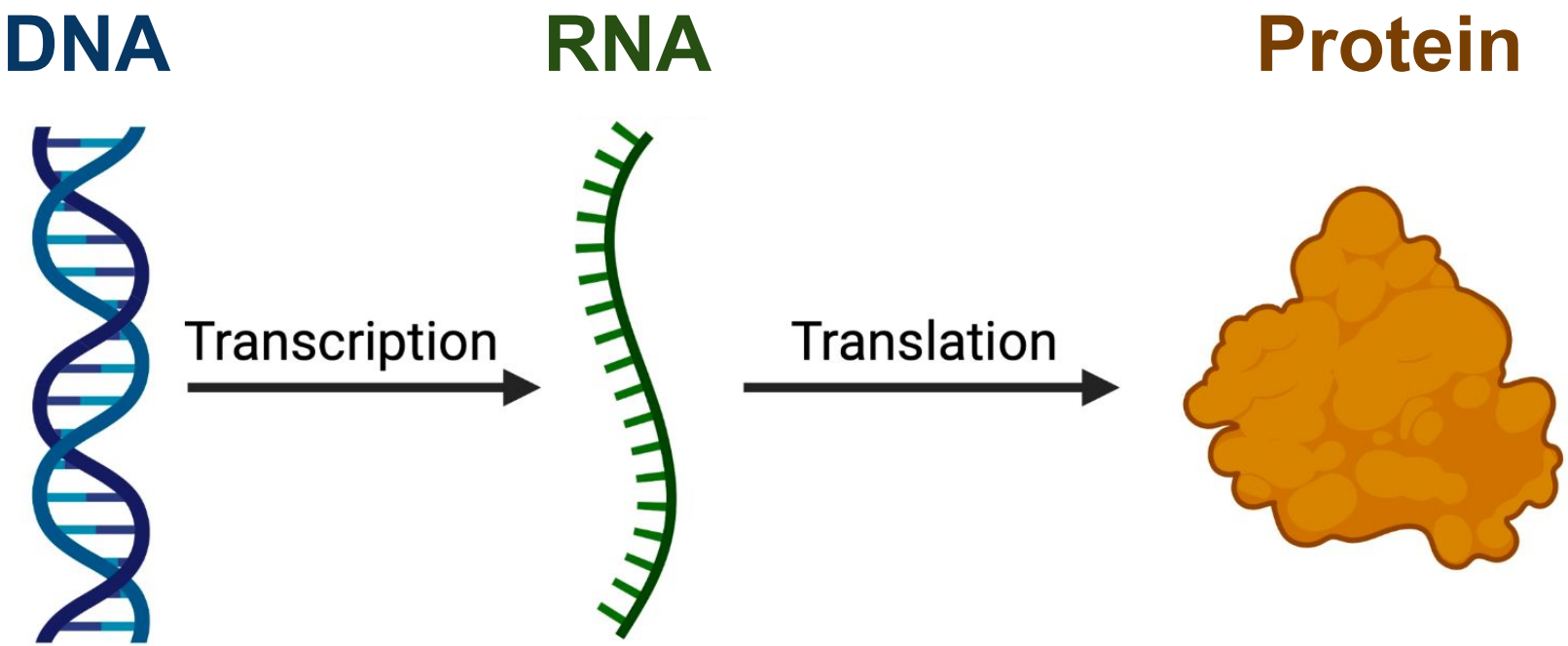
Syl – Greek prefix for together

Definition: The biological process of attaching sugars to a target molecule (such as a protein)

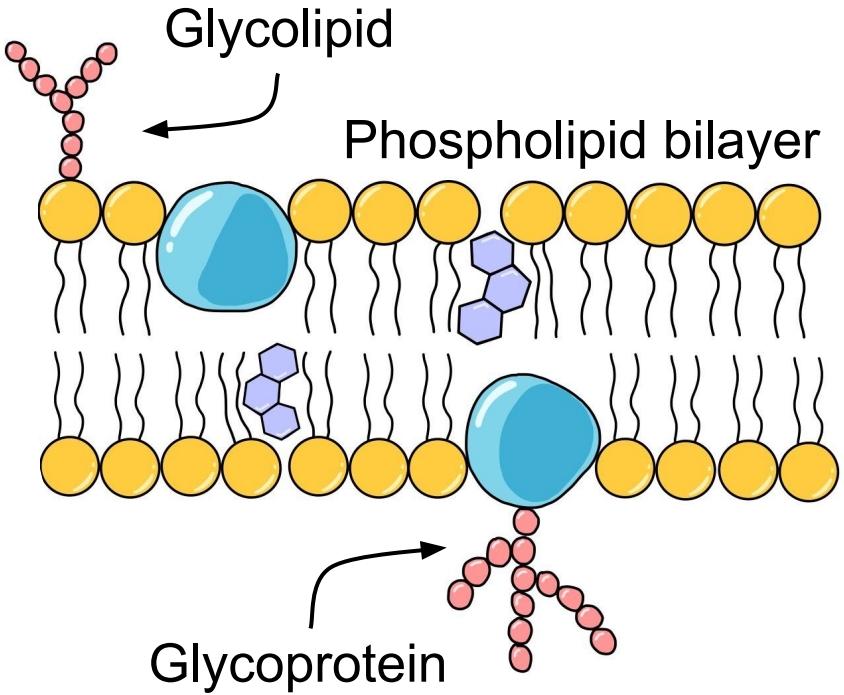
If we say a word that's unclear, let us know!

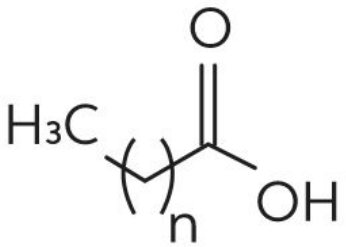

Fundamentals of sugar coat creation

The Central Dogma is a crucial tenet of biology

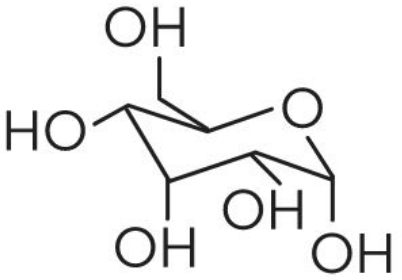


There are 4 building blocks of human biology



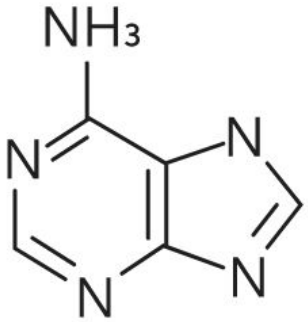


Fatty acids

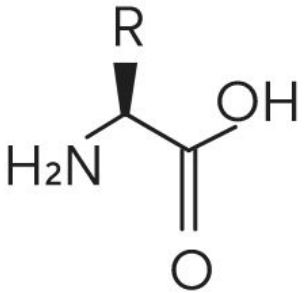


Carbohydrates

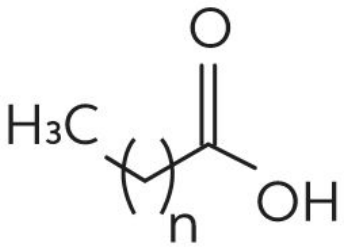
There are 4 building blocks of human biology



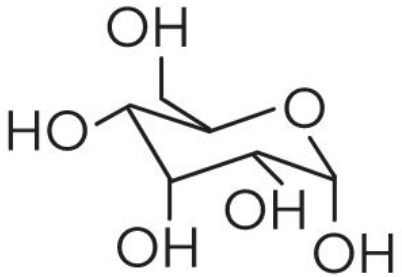
Nucleobases



Amino acids



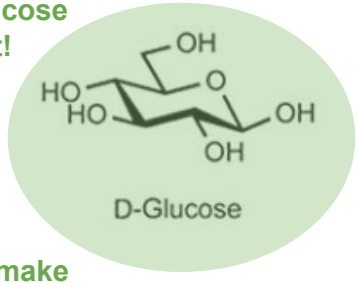
Fatty acids



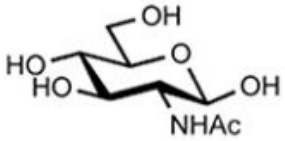
Carbohydrates

There are 9 sugar building blocks (monomers) in us!

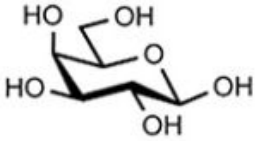
You require glucose in your diet!



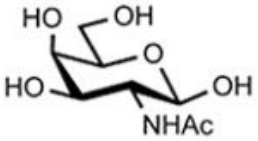
D-Glucose



N-Acetyl-D-glucosamine

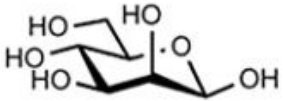


D-Galactose

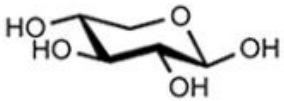


N-Acetyl-D-galactosamine

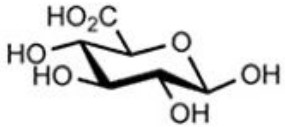
Your cells can make the remaining 8 single sugars from glucose



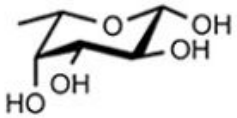
D-Mannose



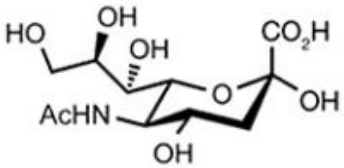
D-Xylose



D-Glucuronic acid



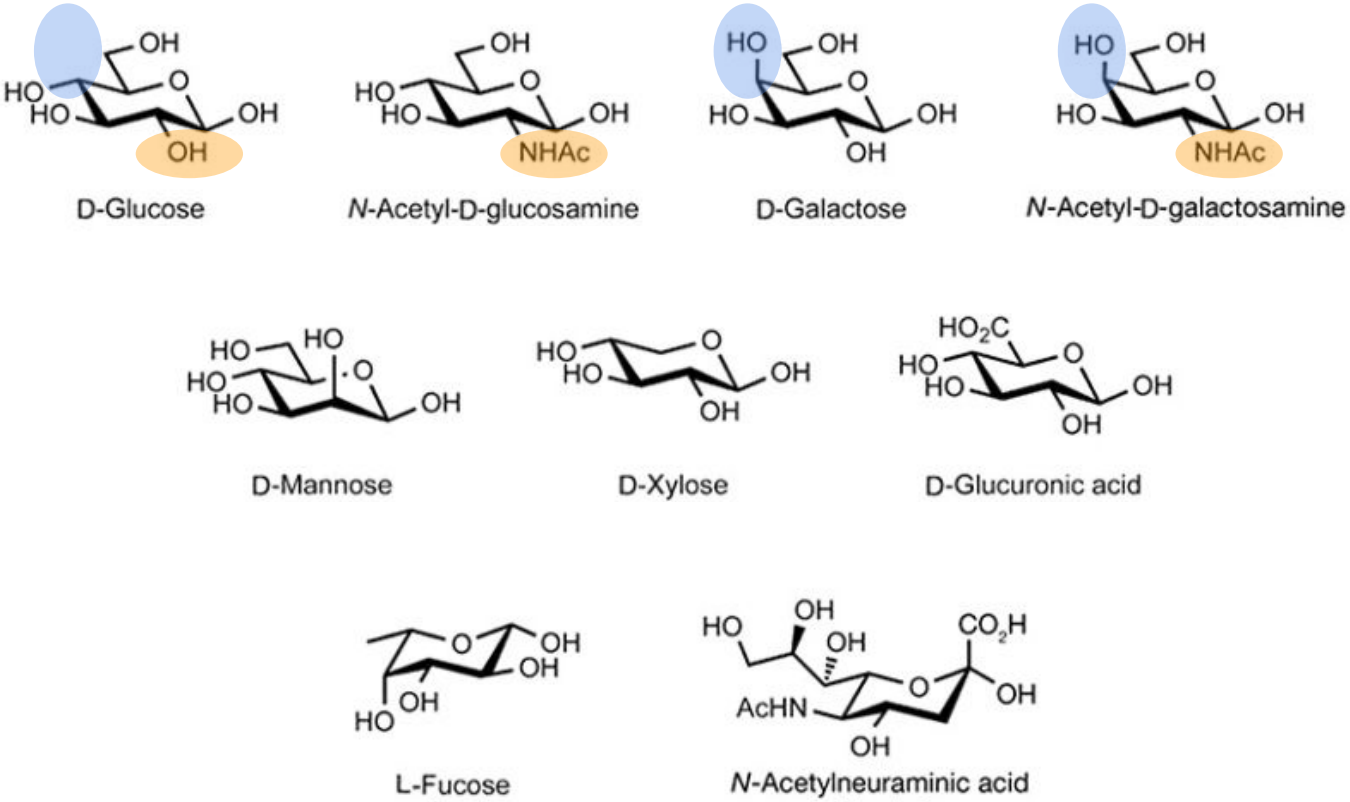
L-Fucose



N-Acetylneuraminic acid

Seeberger. 2022. *Cold Spring Harbor Laboratory Press.*

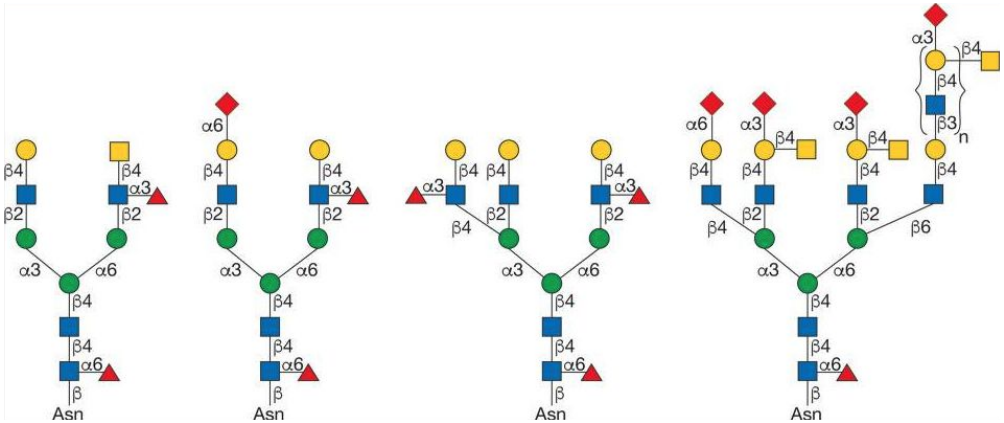
There are 9 sugar building blocks (monomers) in us!

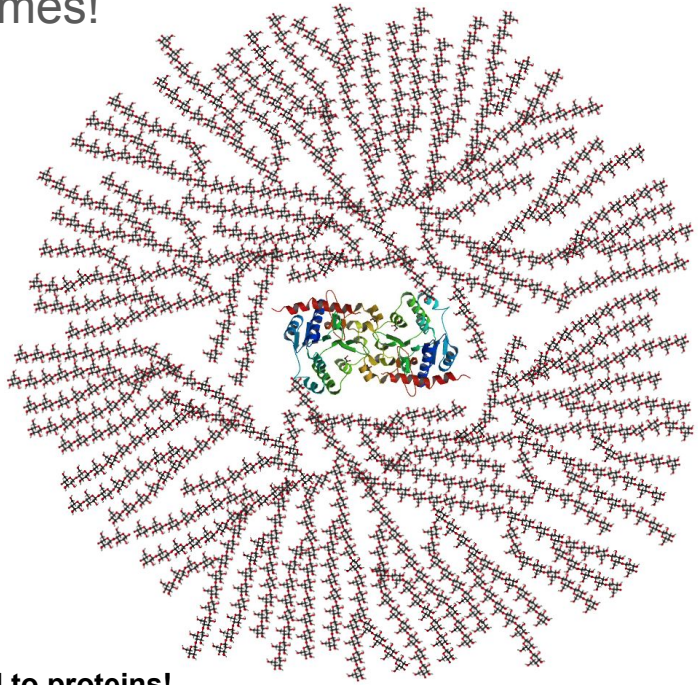


Seeberger. 2022. *Cold Spring Harbor Laboratory Press.*

Unlike DNA, RNA, and protein polymers, sugar polymers:

1. Do not have a template: built wholly by enzymes!
2. Can be incredibly branched and diverse!





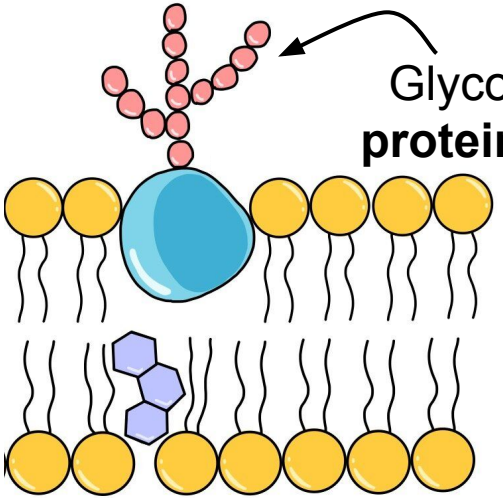
All sugars shown here are attached to <u>proteins</u>!

Seeberger. 2022. *Cold Spring Harbor Laboratory Press.*

Why do we care about sugar-modified proteins (glycoproteins)?

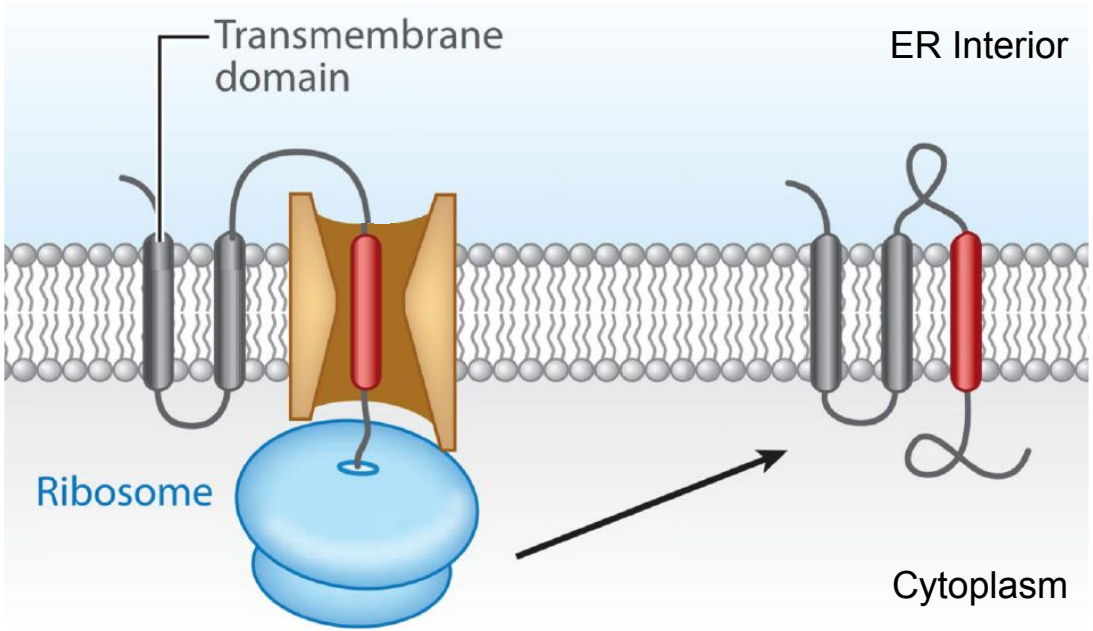
50% of proteins in your cells are glycosylated!

The glycoproteins that cells put on their plasma membranes **help define those cells!**



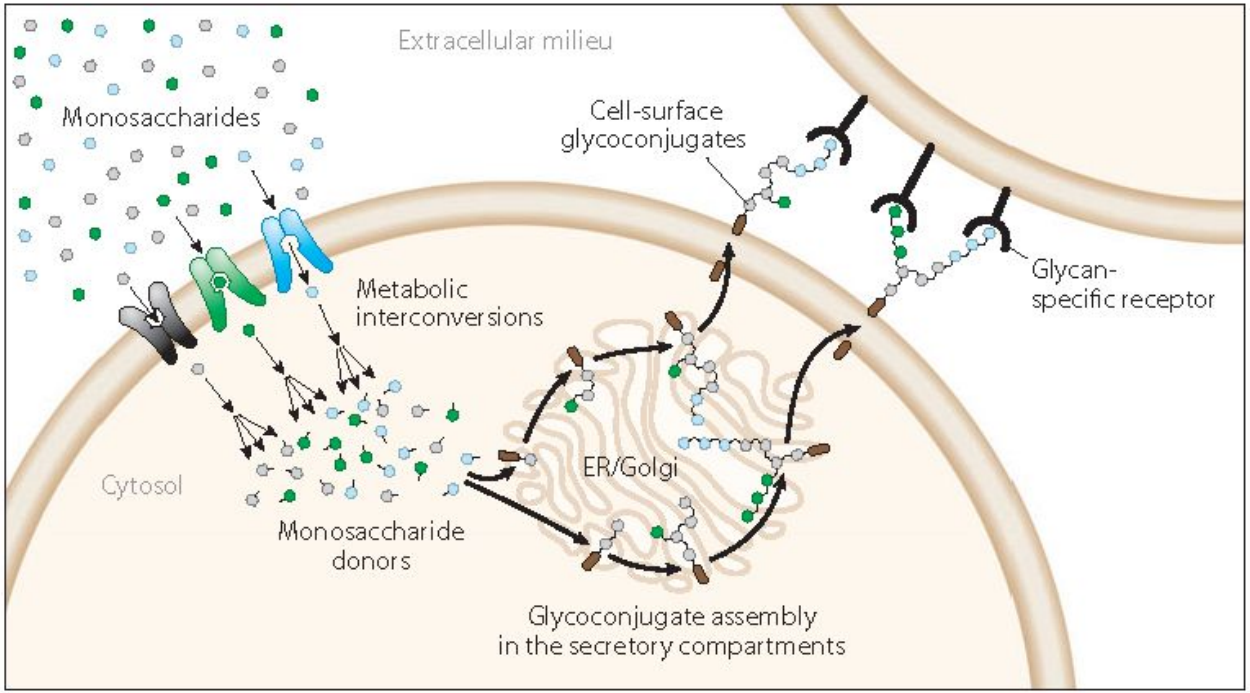
Glycoprotein: most are **membrane proteins, not freely floating in cells**

Membrane proteins are made in the endoplasmic reticulum



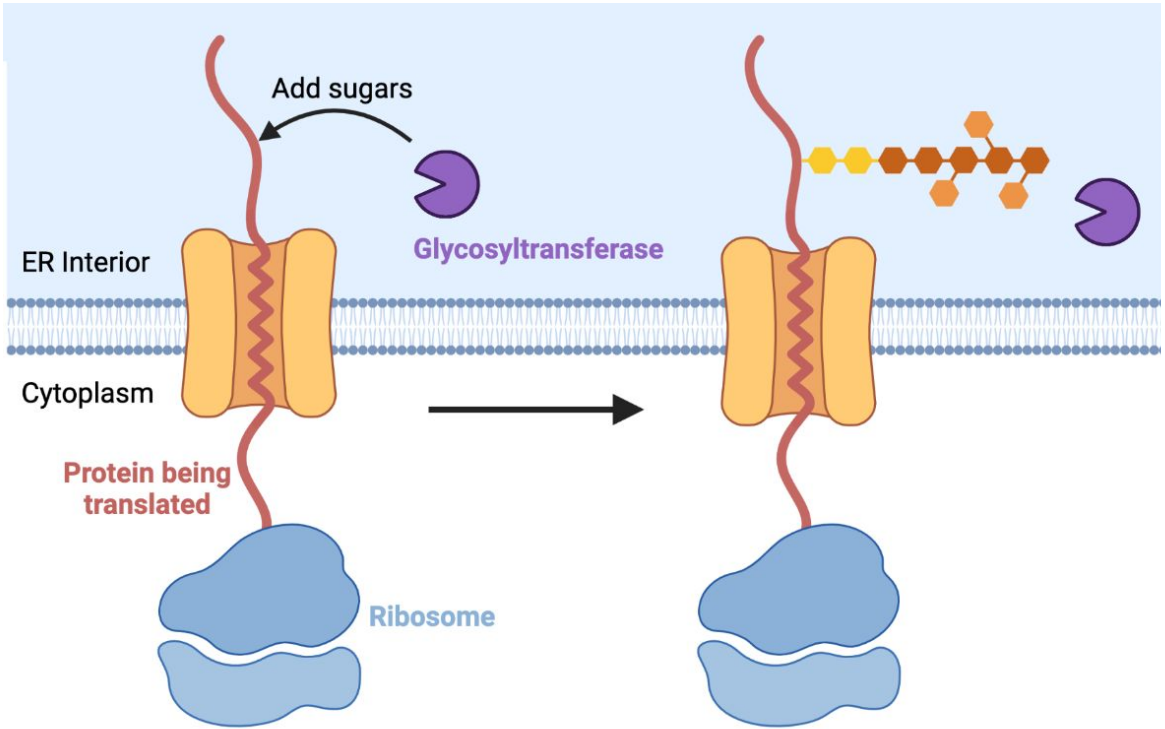
Shao & Hegde. 2014. *Annu Rev Cell Dev Biol.*

Membrane proteins are modified with sugars in the endoplasmic reticulum and golgi



Kiessling & Splain. 2010. *Annu Rev Biochem.*

Enzymes catalyze sugar/protein modifications



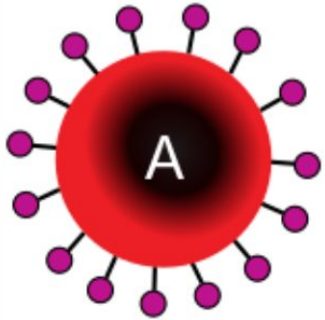
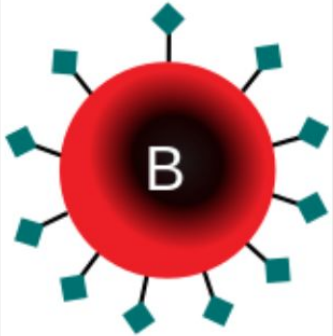
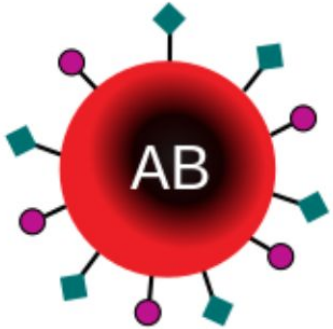
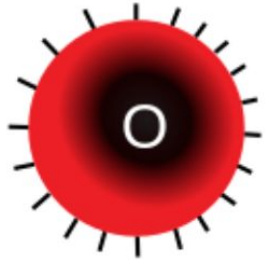
Fundamentals of sugar coat creation

- There are 9 carbohydrate building blocks (**monomers**) for humans
- Enzymes combine these monomers to form complex, branched carbohydrate **polymers**
- Many of these carbohydrate polymers are attached to proteins, making **glycoproteins**
- Glycoproteins are most often embedded in the **cell membrane**
- These glycoproteins are made in the **endoplasmic reticulum and golgi** and transported to the cell surface, where they make a **sugar coat**

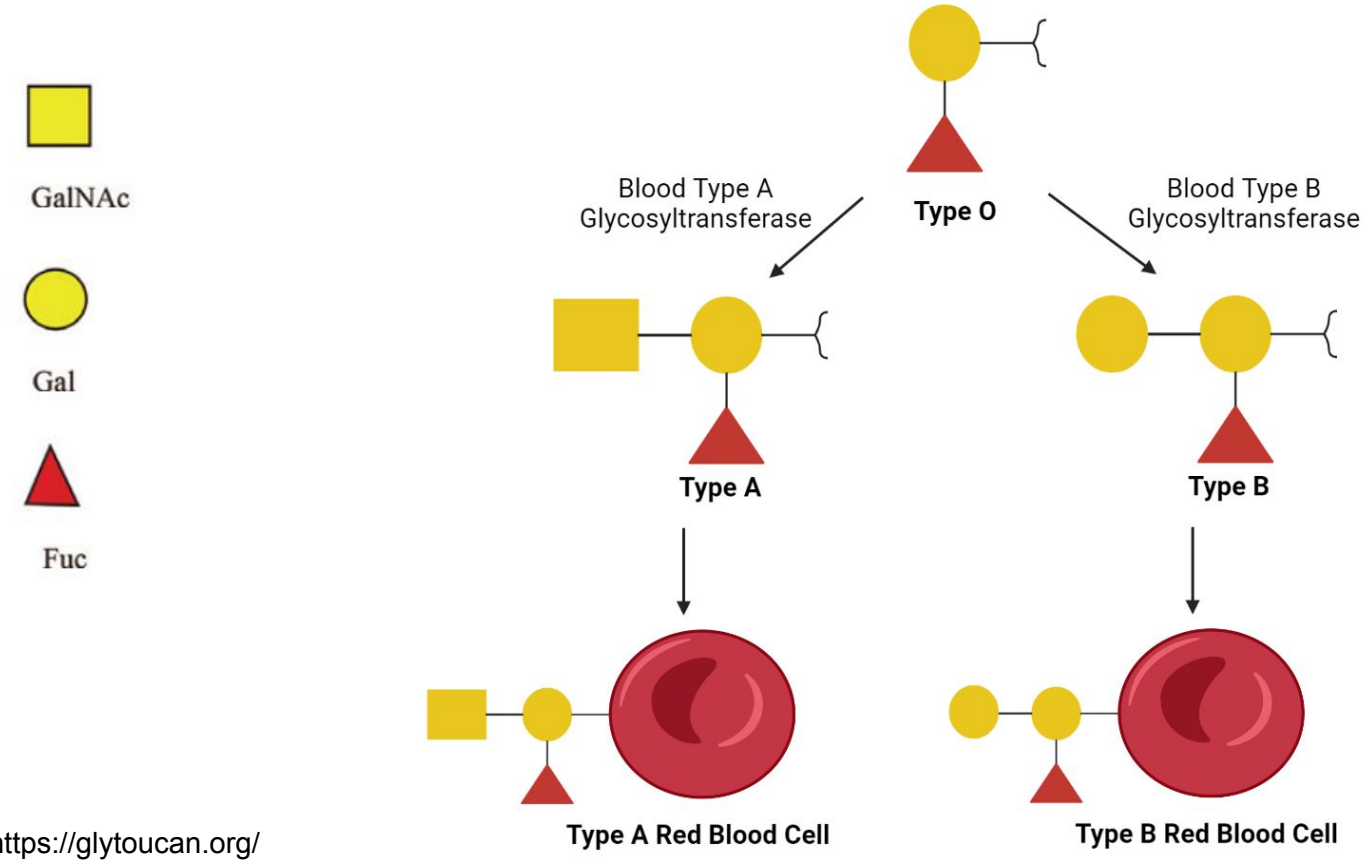
What do these sugar coats **do**?


Sugar coats and **your blood type**

Basics of Blood Type

	Group A	Group B	Group AB	Group O
Red blood cell type				

How do sugars help define your blood?

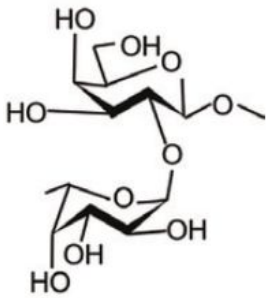


https://glytoucan.org/

Dotz & Wuhrer. 2016. *Biochimica et biophysica acta*.

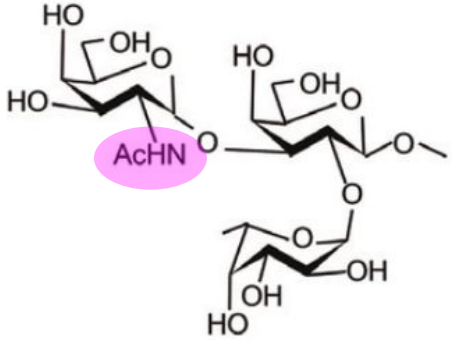
Type A and Type B blood groups are defined by a difference in **one** chemical linkage

Fucα1-2Galβ-



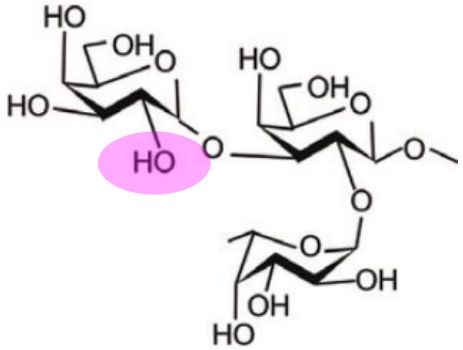
Type O

GalNAcα1-3[Fucα1-2]Galβ-



Type A

Galα1-3[Fucα1-2]Galβ-

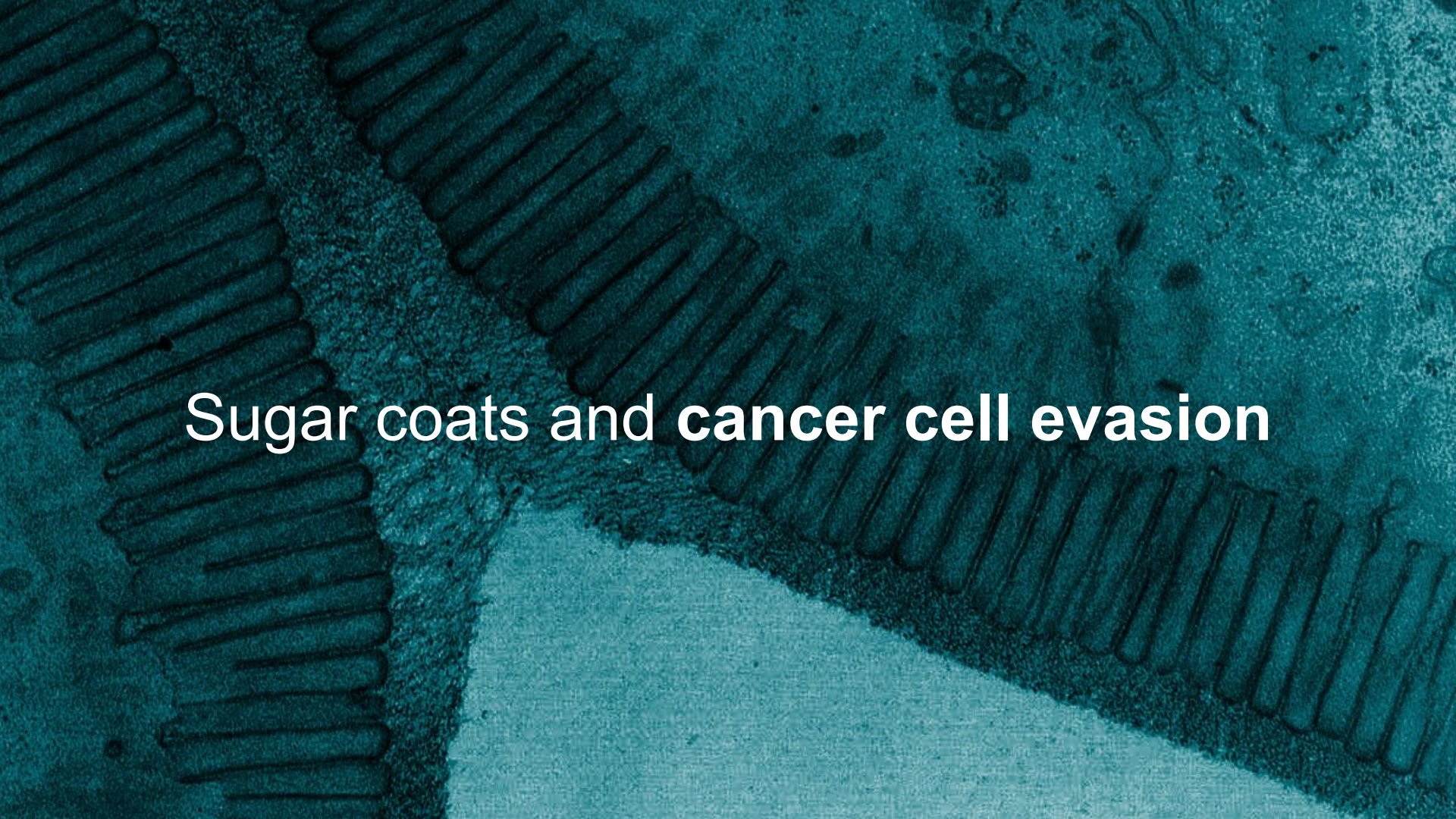


Type B

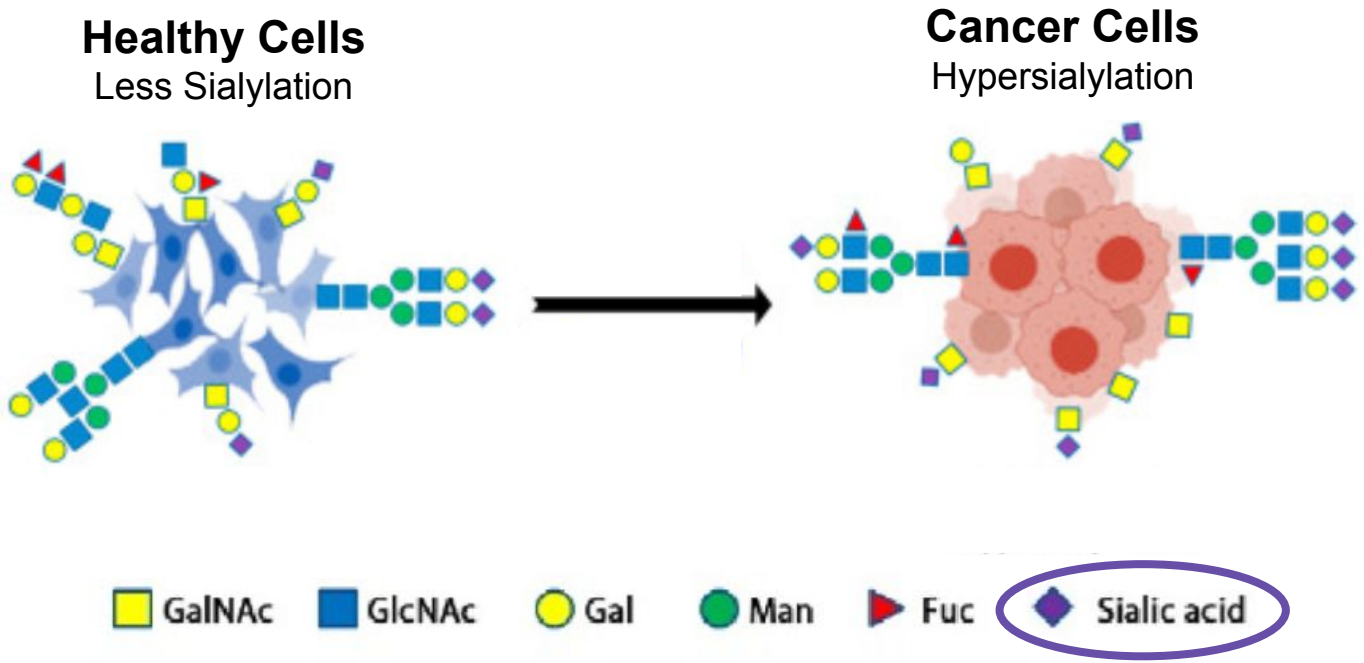
https://glytoucan.org/
Dotz & Wuhrer. 2016. *Biochimica et biophysica acta*.

Sugar coats and **your blood type**

- The sugars on the **surface** of your red blood cells determine your blood type
- The Type A and Type B sugars differ by **one** chemical group!
- These sugars are added based on the presence or absence of **specific enzymes** inherited from your biological parents


Sugar coats and **cancer cell evasion**

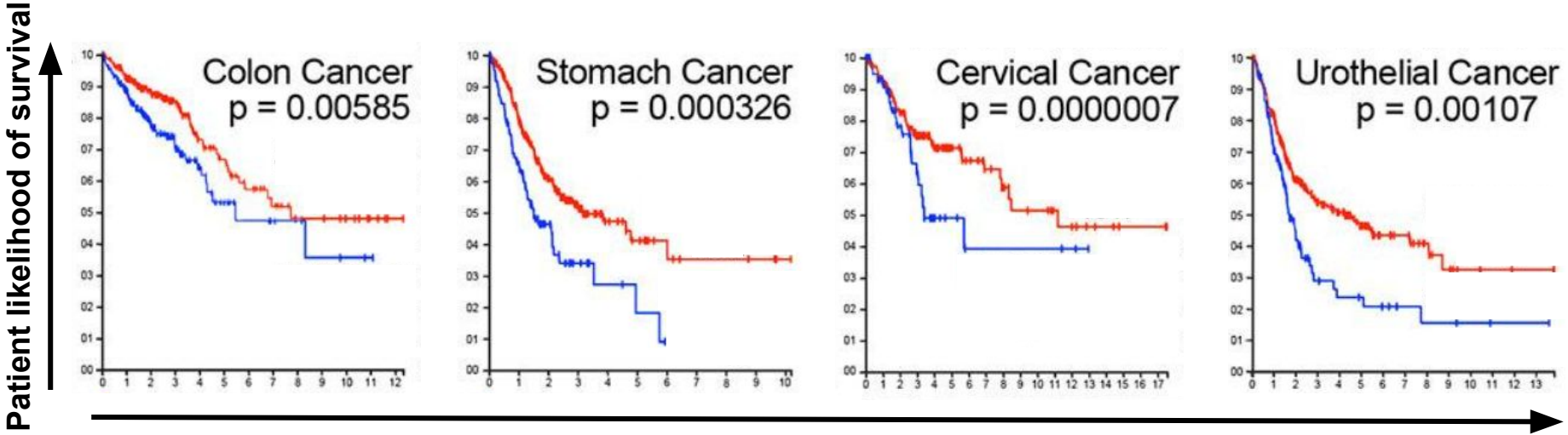
Some Cancer Cells Display More Sialic Acid on their Cell Surface



Gao, Ziyuan, et al. 2021 *Current Research in Pharmacology and Drug Discovery.*

Hypersialylation of cancer cells leads to a higher likelihood of patient death

Red bars: patients with less sialic acid sugar on their cancer cells
Blue bars: patients with more sialic acid sugar on their cancer cells



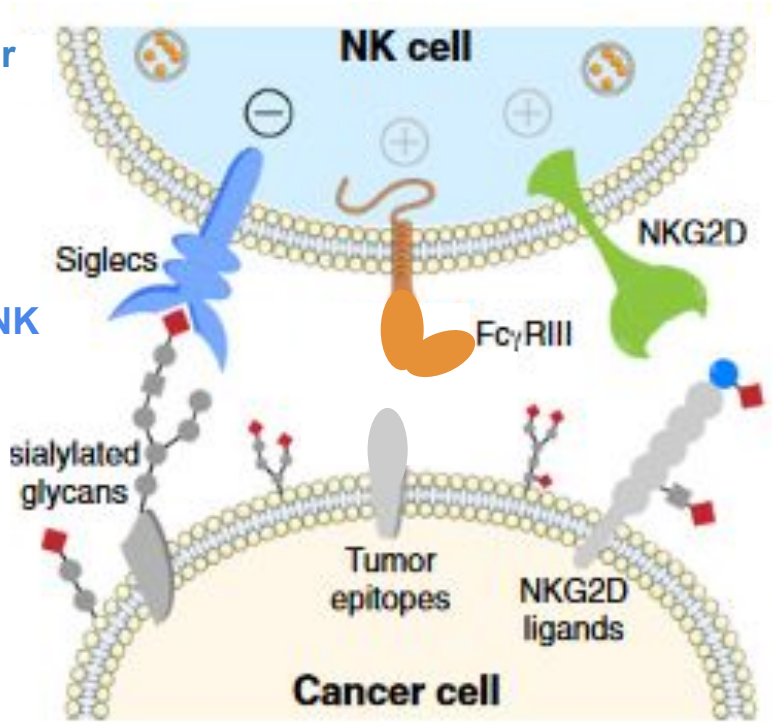
Cancer is more deadly when it has more sialic acid sugar on its surface.

Friedman, David J., et al. 2021. *Cancer Immunology Research.*

Sialic acid helps cancer cells by allowing them to hide from natural killer (NK) cells

NK cells help clear cancer cells

Sialic Acid binds Siglecs and block NK cell activation



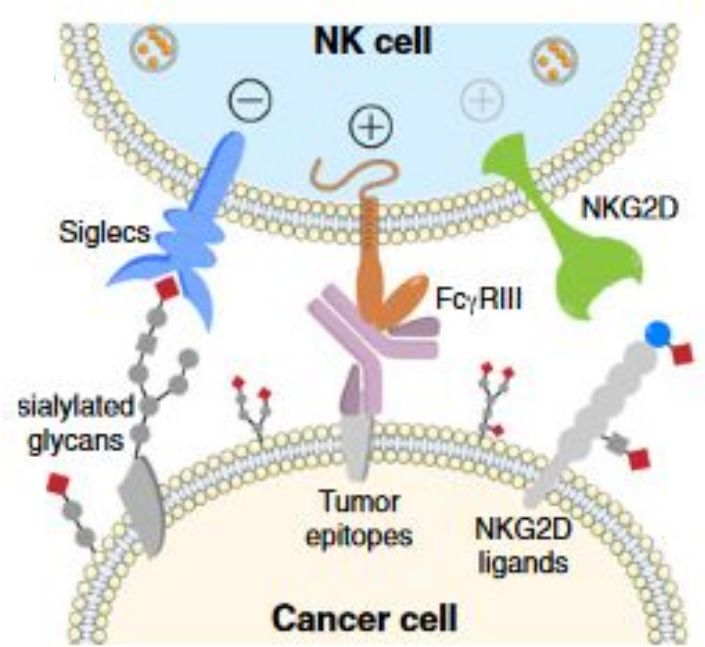
Activated Siglecs bind NKG2D and prevent it from being activated.

How could we help NK cells recognize hypersialylated cancer cells?

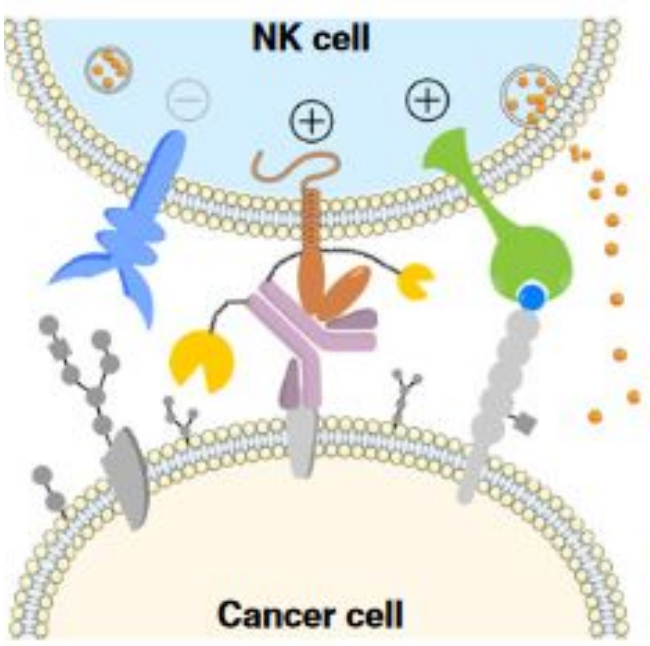
Xiao, Han, et al. 2016. *PNAS.*

Cancer treatment approach: **mow down sialic acid** on cancer cells

Current treatments: use an antibody that links NK to HER2 cancer cells

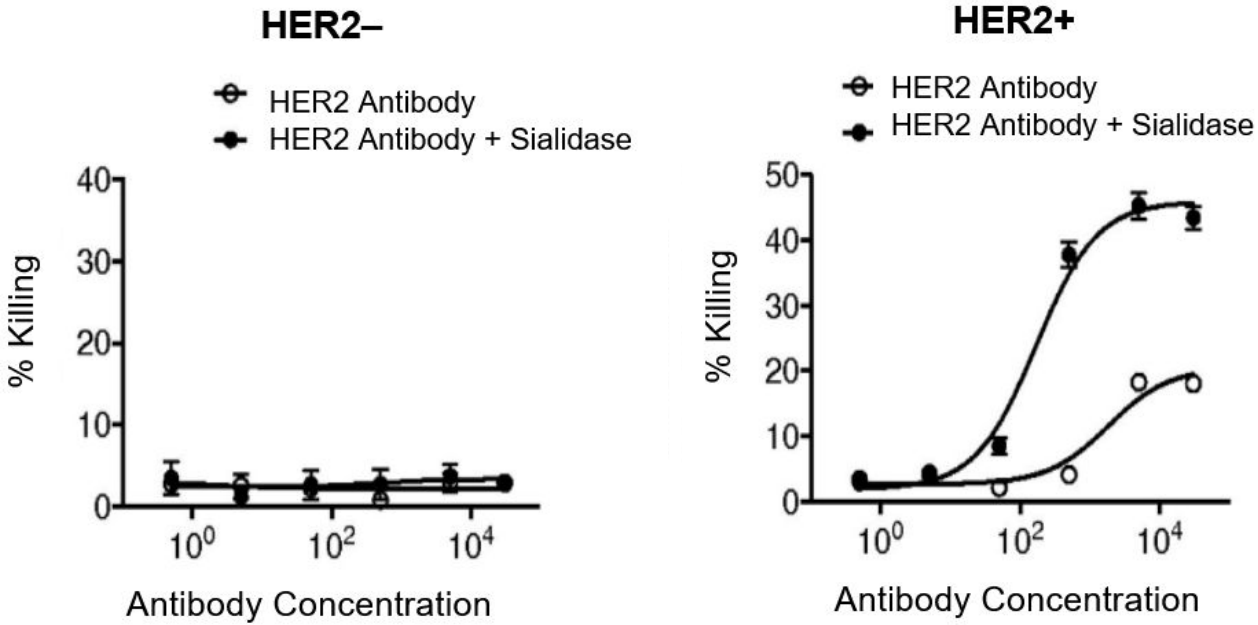


New idea: use an antibody that links NK to HER2 cancer cells AND is fused to Sialidase



Xiao, Han, et al. 2016. *PNAS.*

How effective is an antibody-mediated sialic acid lawnmower treatment?



Xiao, Han, et al. 2016. *PNAS.*

RECRUITING

ClinicalTrials.gov Identifier: NCT05259696

Glycan Mediated Immune Regulation With a Bi-Sialidase Fusion Protein (GLIMMER-01) (GLIMMER-01)

Information provided by Palleon Pharmaceuticals, Inc. (Responsible Party)

Last Updated: September 20, 2022

beta.clinicaltrials.gov/study/NCT05259696

Sugar coats and **cancer cell evasion**

- Many cancer cells have more **sialic acid** in their sugar coats
- Cancers with more sialic acid in their sugar coats have a **higher likelihood** of killing patients
    - This is because sialic acid **blocks** NK cells from killing the cancer cells
- In 2016, scientists created a therapeutic to **selectively mow down sialic acid** coatings in cancer cells
- This therapeutic is now in **Stage I clinical trials!!!**

Sugars give us energy **and so much more!**

How sugar coats get made!

What do these sugar coats do!

- Define blood type
- Cancer cell evasion → now in clinical trials!
- **So many other amazing things we didn’t cover today!!**

Resources

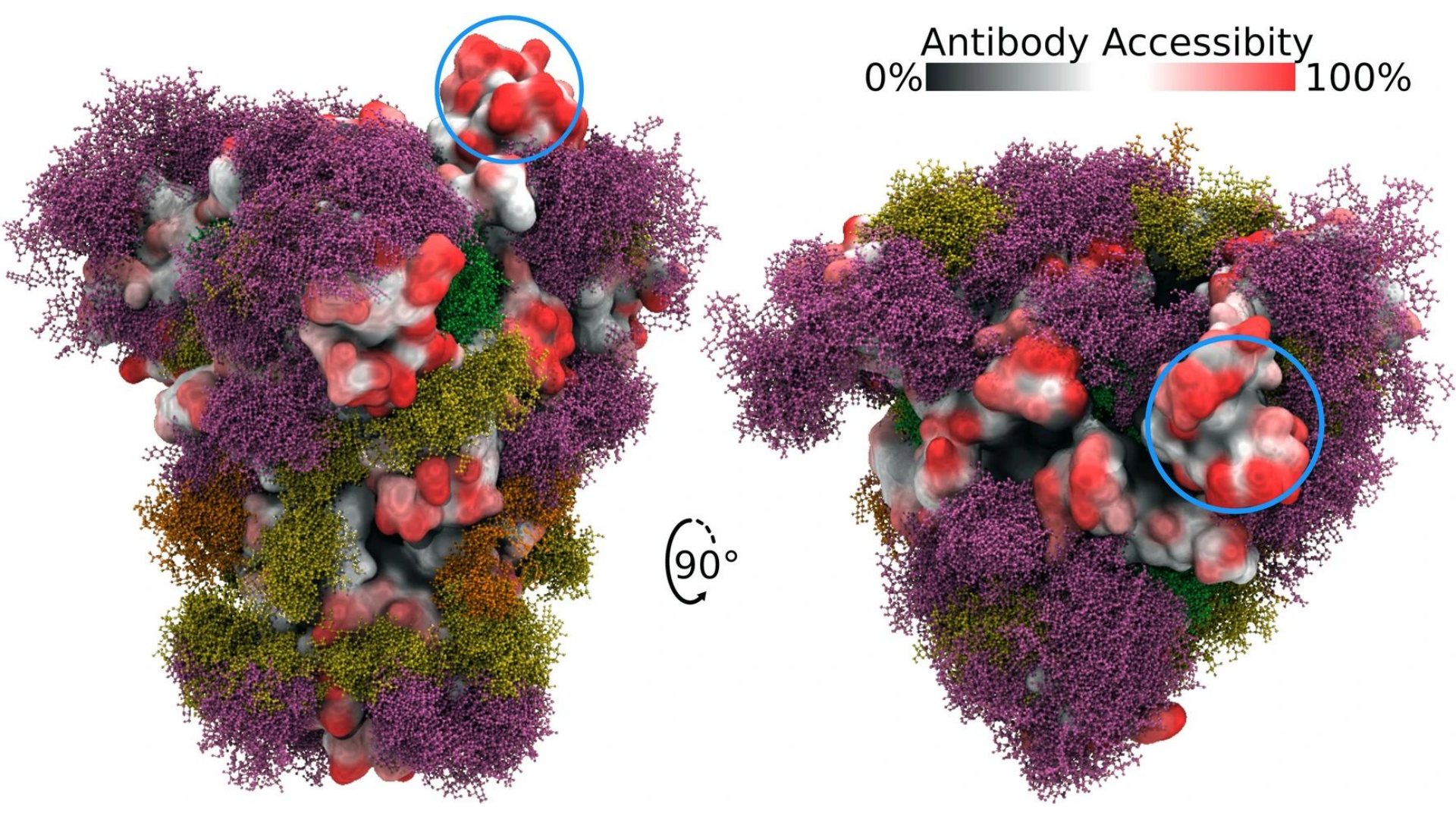
iBiology.org: Carolyn Bertozzi (Nobel Prize Winner in Chemistry for 2022!)

Free essentials of glycobiology textbook: tinyurl.com/glycobio

We're sticking around for questions!

- Anything we covered today
- Glycobiology generally
- Biology or biomedical research
- Getting a PhD in biology/STEM
- This background image of the glycosylated SARS-CoV-2 spike protein!

Grant, Oliver C., et al. 2020. *Scientific Reports*. 10.1: 1-11


Antibody Accessibity
0%
100%
90°

Scientific papers we cited - if you can’t find them, email us!

- Dotz, V., & Wuhrer, M. (2016). Histo-blood group glycans in the context of personalized medicine. *Biochimica et biophysica acta*, *1860*(8), 1596–1607. https://doi.org/10.1016/j.bbagen.2015.12.026
- Friedman, David J., et al. "ST8Sia6 Promotes Tumor Growth in Mice by Inhibiting Immune Responses." *Cancer immunology research* 9.8 (2021): 952-966
- Gao, Z., Xu, M., Yue, S., Shan, H., Xia, J., Jiang, J., & Yang, S. (2021). Abnormal sialylation and fucosylation of saliva glycoproteins: Characteristics of lung cancer-specific biomarkers. *Current research in pharmacology and drug discovery*, 100079.
- Grant, O. C., Montgomery, D., Ito, K., & Woods, R. J. (2020). Analysis of the SARS-CoV-2 spike protein glycan shield reveals implications for immune recognition. *Scientific reports*, *10*(1), 1-11.
- Seeberger PH. Monosaccharide Diversity. In: Varki A, Cummings RD, Esko JD, et al., editors. Essentials of Glycobiology [Internet]. 4th edition. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2022. Chapter 2. https://www.ncbi.nlm.nih.gov/books/NBK579981/ doi: 10.1101/glycobiology.4e.2
- Reid, D. W., & Nicchitta, C. V. (2015). Diversity and selectivity in mRNA translation on the endoplasmic reticulum. *Nature reviews Molecular cell biology*, *16*(4), 221-231
- Xiao, H., Woods, E. C., Vukojicic, P., & Bertozzi, C. R. (2016). Precision glycocalyx editing as a strategy for cancer immunotherapy. *Proceedings of the National Academy of Sciences*, *113*(37), 10304-10309.