Decoding sugar messages to create new diagnostics and therapeutics

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voted second worst traffic in the world

worst city to drive in the world
(BBC)
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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
- Antifreeze proteins

Extract chemical mechanisms of function

- Antibiotics against resistant infections
- Cryoprotectants to preserve tissues
sugars | glycans
nutrition vs information
glycans are among the biomolecules of life

proteins

nucleic acids (DNA/RNA)

lipids

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

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Building Block</th>
<th>Approximate Mass</th>
<th>Possible Variations in a Trimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Amino acids</td>
<td>$125 \to 10^4-10^5$</td>
<td>6</td>
</tr>
<tr>
<td>Nucleic Acid</td>
<td>Nucleotides</td>
<td>$330 \to 10^3-10^5$</td>
<td>6</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Monosaccharides</td>
<td>$200 \to 10^2-10^6$</td>
<td>1,056 to 27,648!</td>
</tr>
</tbody>
</table>
glycan building blocks are depicted as colored symbols

<table>
<thead>
<tr>
<th>SHAPE</th>
<th>White (Generic)</th>
<th>Blue</th>
<th>Green</th>
<th>Yellow</th>
<th>Orange</th>
<th>Pink</th>
<th>Purple</th>
<th>Light Blue</th>
<th>Brown</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filled Circle</td>
<td>Hexose</td>
<td>Glc</td>
<td>Man</td>
<td>Gal</td>
<td>Glu</td>
<td>All</td>
<td>All</td>
<td>Tal</td>
<td>Ido</td>
<td></td>
</tr>
<tr>
<td>Filled Square</td>
<td>HexNAc</td>
<td>GlcNAc</td>
<td>ManNAc</td>
<td>GalNAc</td>
<td>GalNAc</td>
<td>AllNAc</td>
<td>AllNAc</td>
<td>TalNAc</td>
<td>IdoNAc</td>
<td></td>
</tr>
<tr>
<td>Crossed Square</td>
<td>Hexosamine</td>
<td>GlcN</td>
<td>ManN</td>
<td>GalN</td>
<td>GalN</td>
<td>AllN</td>
<td>AllN</td>
<td>TalN</td>
<td>IdoN</td>
<td></td>
</tr>
<tr>
<td>Divided Diamond</td>
<td>Hexuronate</td>
<td>GlcA</td>
<td>ManA</td>
<td>GalA</td>
<td>GalA</td>
<td>AllA</td>
<td>AllA</td>
<td>TalA</td>
<td>IdoA</td>
<td></td>
</tr>
<tr>
<td>Filled Triangle</td>
<td>Deoxyhexosyl</td>
<td>Quil</td>
<td>Rha</td>
<td>6dGul</td>
<td>6dAll</td>
<td>6dTal</td>
<td>6dTal</td>
<td>Fuc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divided Triangle</td>
<td>DeoxyhexNAc</td>
<td>QuilNAc</td>
<td>RhaNAc</td>
<td>6dAllNAc</td>
<td>6dTalNAc</td>
<td>FucNAc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat Rectangle</td>
<td>Di-deoxyhexose</td>
<td>GlcI</td>
<td>Tyv</td>
<td>Abe</td>
<td>Par</td>
<td>Dig</td>
<td>Col</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filled Star</td>
<td>Pentose</td>
<td>Ara</td>
<td>Lyx</td>
<td>Xyl</td>
<td>Rib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filled Diamond</td>
<td>Deoxynuroinosyl</td>
<td>Kdn</td>
<td>NeuS</td>
<td>NeuS</td>
<td>Neu</td>
<td>Sia</td>
<td></td>
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<tr>
<td>Flat Diamond</td>
<td>Deoxynuroinosyl</td>
<td>Pse</td>
<td>Leg</td>
<td>Aci</td>
<td></td>
<td>4eLeg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat Hexagon</td>
<td>Unknown</td>
<td>Bac</td>
<td>LDMannHep</td>
<td>Kdo</td>
<td>Dha</td>
<td>MurNAc</td>
<td>MurNGc</td>
<td>Mur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentagon</td>
<td>Assigned</td>
<td>Api</td>
<td>Fru</td>
<td>Tag</td>
<td>Sor</td>
<td>Pal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

glycan building blocks are assembled into other glycans with different messages.
glycan building blocks are assembled into other glycans with different messages

- message X
- message XY
- message Y
- message YZ
- message Z
cell surface glycans dictate blood compatibility

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red blood</strong></td>
<td><img src="image" alt="A" /></td>
<td><img src="image" alt="B" /></td>
<td><img src="image" alt="AB" /></td>
<td><img src="image" alt="O" /></td>
</tr>
<tr>
<td><strong>cell type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td><img src="image" alt="Anti-B" /></td>
<td><img src="image" alt="Anti-A" /></td>
<td>None</td>
<td><img src="image" alt="Anti-A and Anti-B" /></td>
</tr>
<tr>
<td><strong>in Plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antigens</strong></td>
<td><img src="image" alt="A antigen" /></td>
<td><img src="image" alt="B antigen" /></td>
<td><img src="image" alt="A and B antigens" /></td>
<td>None</td>
</tr>
<tr>
<td><strong>in Red Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

InvictaHOG/Wikimedia Commons/Public Domain Image
cell surface glycans dictate blood compatibility
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

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
NOBELPRISET I KEMI 2022
THE NOBEL PRIZE IN CHEMISTRY 2022

Carolyn R. Bertozzi
Stanford University
USA

Morten Meldal
University of Copenhagen
Denmark

K. Barry Sharpless
Scripps Research
USA

"för utveckling av klickkemi och bioortogonal kemi"

"for the development of click chemistry and bioorthogonal chemistry"

#nobelprize
“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
we appreciate complexity

when equipped with the right tools, training, and environment

Huang Research Group
February 2023
we appreciate complexity
when equipped with the right tools, training, and environment
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
discover changes in protein glycosylation
use glycan-binding proteins as message decoders
discover protein glycosylation changes using GBPs as decoders

IN SITU PROXIMITY TAGGING

1
galactin-3 is a glycan-binding protein necessary in hepatic fibrosis

proximity labeling of live hepatic stellate cells

hepatic stellate cells (LX-2)

Gal-3 interacting proteins labeled

discovery of basigin glycoprotein as a messenger for galectin-3

define how & why protein glycosylation is changing
glycomics mass spectrometry reveals glycan patterns
exploit change in protein glycosylation
antibodies and small molecules expedite detection and targeting
Pancreatic ductal adenocarcinoma (PDAC) cancers are lethal.
stromal cancers are lethal and are not efficiently served by current therapies

pancreatic ductal adenocarcinoma (PDAC)
most anticancer therapies target only cancer cells, but the **tumor stroma** promotes resistance to these therapies

Valkenburg (2018) *Nat Rev Clinical Oncology*
proteoglycans in the stroma shield tumors from attack and create signals that tells cancer cells to grow excessively.

*stroma*  
*extracellular (outside of cell*)  
*intracellular (inside of cell*)

*tumor and fibroblast cells*
proteoglycans are pathogenically abundant in metastatic cancers

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

Gill (2016) Histochemistry & Cell Biology
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
Thank you!

Your support gives us momentum to keep pushing the boundaries of science to impact biomedicine.