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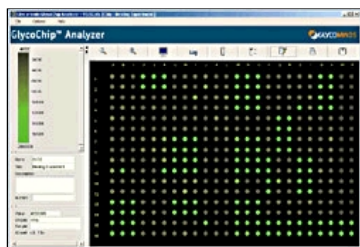
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### Glycobiology Goes to the Ball

New federal funding, new technologies, and a better understanding of carbohydrates' roles in biology have scientists pondering the feasibility of a Human Glycome Project

By Jeffrey M. Perkel

Courtesy of Glycominds Ltd.



**Sweet Spots? One tool glycomics researchers have at their disposal is Glycominds' commercial glycan array. Shown is a screenshot of the GlycoChip Analyzer software used to analyze the chip's data.**

There's more to life than DNA, RNA, and proteins. Literally. Sugars are also in the mix. And the roles that carbohydrates play in biology are just as important as those of any member of the better-characterized trinity. These macromolecules affect cell-cell interactions, immune function, and protein regulation, and disruption of their biology results in disease.

One magazine likened the study of carbohydrates, called glycobiology, to Cinderella's neglected stepsister to her two more glamorous siblings, DNA and protein.<sup>1</sup> Momentum is building, however, to do for carbohydrates what scientists have done for genomes, and are attempting to do for proteomes: to characterize the entire complement of these sugar chains in a cell, called the "glycome." Researchers are guardedly optimistic. According to **Ajit Varki**, professor of medicine and cell and molecular biology, and director of the Glycobiology Research and Training Center at the University of California, San Diego, "we don't know what's

going to happen to Cinderella at midnight."

Scientists acknowledge that sequencing the genome was nothing compared to solving the proteome. Likewise, the glycome will make the proteome seem like child's play. "The problem is that [the glycome is] probably thousands of times as complicated as the genome, in magnitude of complexity and level of diversity," says Varki. First of all, unlike the genetic code, there is no rigid template that accurately specifies glycosylation patterns, but rather a complex assembly-line system involving competition by hundreds of gene products. In addition, each cell, tissue, organ, and organism exhibits different glycosylation patterns, which can change based on the cell's state or activity. Further, proteins often have numerous glycosylation sites, each of which may have a different carbohydrate group attached, and these sugar chains can themselves be modified.

The sugar chains' structures are also problematic; some are linear, but many are branched. And unlike with DNA and protein, the inter-monomeric linkages are not constant. Thus, multiple iterative methods are usually needed to fully define a given glycan structure. These various factors offer "totally new challenges that most biopolymer analytical people have yet to fret with," says **Vernon Reinhold**, a chemistry professor at the University of New Hampshire who coined the word glycome.

**Richard Cummings**, professor of biochemistry and molecular biology and director, Oklahoma Center for Medical Glycobiology at the University of Oklahoma Health Sciences Center, points out several additional complications. Unlike DNA, there is no way to amplify carbohydrates. If a researcher wants to obtain more of an interesting sugar, the options are either to synthesize that structure, or isolate more of the material from tissue. But most of the interesting carbohydrates identified thus far are minor species. "It's like looking at a mountain range like the Himalayas. It's easy to see the peaks, but the problems are down in the valleys," he says. And it won't be easy to determine when the entire glycome is solved, in contrast to the human genome project, in which "you would know at some point [that] you've covered it from A to Z," observes Cummings.

### Critical Carbs

Carbohydrates and carbohydrate-binding proteins (CBPs) mediate a number of essential functions. The class of CBPs called selectins, for instance, regulates leukocyte trafficking in various ways. When a tissue becomes inflamed, the endothelial cells lining blood vessel walls begin to express P-selectin, which recognizes a carbohydrate structure called sialyl-Lewis-X (SLX) along with tyrosine sulfate residues on the P-selectin glycoprotein ligand-1 (PSGL-1). Neutrophils express this molecule, and as they pass over the endothelial cells, the interaction between P-selectin and its ligand slows and finally stops the cells. The neutrophils can then burrow between the endothelial cells to attack the infection in the tissue.

CD22, which is part of the B-cell receptor (BCR) complex, is another critical CBP. CD22 doesn't affect leukocyte trafficking, but rather, receptor signaling pathways. This protein negatively regulates the BCR, preventing accidental activation of the cell in response to "self" antigens and inhibiting autoimmune disease. Mice that lack the sialyltransferase required to produce CD22's ligand are profoundly immunosuppressed, suggesting that in normal cells, the CD22 ligand removes the receptor from the BCR complex, enabling the BCR to activate the cell.

Several human diseases result from faulty carbohydrate metabolism. Tay-Sachs disease, Sandhoff disease, and juvenile GM2 gangliosidosis are related carbohydrate degradation disorders that result from hexosaminidase deficiency. Congenital Disorders of Glycosylation (CDG) and Leukocyte Adhesion Deficiency (LAD) are related to faulty carbohydrate synthesis. They appear to be extremely rare: the most common form of CDG, which results from a defect in the phosphomannomutase (*PMM2*) gene, affects perhaps 200 individuals worldwide, according to **Donna**



ahead. For his part, Paulson is confident that the consortium can make real progress in the next five years. But, "Will we finish everything there is to be known about glycobiology? No, I don't think so," he says. Cummings concurs: "We may not define the glycome, but we're going to know a lot about the functions of carbohydrates."

And that will surely yield clinical benefits. According to Krasnewich, researchers now understand that type 1b CDG is caused by a phosphomannose isomerase deficiency. Doctors can treat these patients simply by bypassing the affected step in carbohydrate biosynthesis. And how do they do that? With a pinch of sugar! In this case, mannose.

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#### References

1. S. Hurlley et al., "Cinderella's coach is ready," *Science*, 291:2337, March 23, 2001.
2. A. Dell, H.R. Morris, "Glycoprotein structure determination by mass spectrometry," *Science*, 291:2351-6, March 23, 2001.
3. G. Venkataraman et al., "Sequencing complex polysaccharides," *Science*, 286:537-42, 1999.

#### Selected Glycomics Resources

- The Consortium for Functional Glycomics [glycomics.scripps.edu](http://glycomics.scripps.edu)
- Glycobiology Research and Training Center [grtc.ucsd.edu](http://grtc.ucsd.edu)
- Glycomics Database [www.glycomics.com](http://www.glycomics.com)
- GlycoMinds Ltd. [www.glycominds.com](http://www.glycominds.com)
- GlycoSuite Database [www.glycosuite.com](http://www.glycosuite.com)
- Society for Glycobiology [www.glycobiology.org](http://www.glycobiology.org)

#### Supplemental Materials



[Suppliers of General Glycobiology Research Reagents](#)



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