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Sugar Medicine

Researchers are finding drug leads as they tease out pathways of cellular glycosylation

Stu Borman

THE ATTACHMENT of sugars to proteins or lipids in cells is one of the most difficult molecular modifications to study because sugar structures are so complex and variable. But researchers are steadily overcoming the obstacles involved, and their efforts have made it increasingly clear that glycosylation, as this class of reactions is known, plays key roles in human health and disease.



Martin De Kort

Longer Action Organon researchers used a linker (jagged chain) to conjugate insulin (top) with a pentasaccharide (center) that binds the plasma carrier protein antithrombin III (ribbon structure). The conjugate remains active longer in the bloodstream than insulin.

"Carbohydrate structures are absolutely critical for biological activity," says professor of biochemistry and molecular biology Michael Pierce of the University of Georgia, Athens. "So we can't ignore glycosylation."

Researchers working at the interface between glycosylation and drug discovery indeed have been working hard to better understand the physiological effects of changes in biomolecular glycosylation and to devise better ways to diagnose and treat conditions that arise when glycosylation goes awry.

Glycosylation goes wrong, for instance, in a number of human diseases caused by malfunctions in the synthesis or breakdown of complex sugar structures, or glycans. Scientists are trying to find out more about the mechanisms that underlie these conditions so drugs can be designed to treat patients that have them. Researchers have also been developing finesse in glycosylation chemistry to create libraries of drug candidates, to improve drug properties, and even to modify the behavior of whole cells.

The first use of glycoproteins as drugs goes back to the 1980s, and recently major drug companies have been buying small biotech companies that specialize in creating glycoproteins with glycans tailored for specific biomedical jobs.

The financial scale of some of these acquisitions attests to the growing importance of glycans in drug discovery. In 2005, for example, Roche paid about \$180 million to acquire Zurich-based GlycArt Biotechnology, which specialized in boosting the potency of therapeutic antibodies by glycosylating them in specific ways. And last year, Merck paid \$400 million for GlycoFi, a Lebanon, N.H.-based firm that developed a yeast-based approach for optimizing sugar structures on therapeutic glycoproteins to improve the glycoproteins' efficacy, duration of action, and specificity.

The latest findings and progress on glycan-related drug discovery was the focus of the Benzon Symposium on Glycosylation: Opportunities in Drug Development, in Copenhagen last month. The meeting was organized by carbohydrate chemist Ole Hindsgaul and enzymologist Monica M. Palcic of Carlsberg Laboratory, in Copenhagen, and glycobiologist Henrik Clausen and medicinal chemist Povl Krogsgaard-Larsen of Copenhagen University. The symposium was funded by the Alfred Benzon Foundation, a Copenhagen-based organization that supports the medical and pharmaceutical sciences and related areas by sponsoring fellowships and symposia.

Prominent on the symposium's agenda was a set of glycan-related conditions—congenital disorders of glycosylation (CDGs)—that cause human disease and death but are hardly recognized by the mainstream biomedical community. CDGs are caused by genetic defects that interfere with the glycosylation of proteins in the body. The first patients with this clinical syndrome were identified in 1980. Now, more than 35 CDGs are known.

"CDGs are underdiagnosed because most physicians do not know about them," said Hudson Freeze, director of glycobiology at the Burnham Institute for Medical Research, La Jolla, Calif.

"CDGs are incredibly rare diseases," commented Gerald Hart, director of biological chemistry at Johns Hopkins University School of Medicine, who chaired a Benzon session. "The reason they're rare is that most people who have a genetic defect in any of the glycosylation pathways die while they're embryos." Patients who survive are those who retain sufficient residual glycosylation activity in the defective pathway.

Only about 600 patients worldwide have ever been diagnosed with CDGs. Symptoms are mild to severe and range from neurological disorders and changes in body shape to blood-clotting problems and liver and kidney disease.



Hudson Freeze, reprinted from *Glycobiology* **2001**, *11*, 129R, by permission of oxford university press

Flawed Sugars CDGs are often-fatal glycosylation-pathway diseases that cause a variety of errors in the normal structures (left) of glycans on proteins (black curves), such as unoccupied glycosylation sites (center) and missing sugars on some glycan branches (right).

Therapies are available for only two CDGs. Oral supplements of mannose are effective for patients deficient in phosphomannose isomerase, and some patients with defects in intracellular transport of activated fucose respond to dietary administration of this sugar.

Some cases of muscular dystrophy are also CDG-related, said Tamao Endo, leader of the glycobiology research group at Tokyo Metropolitan Institute of Gerontology. Researchers discovered in 1987 that errant forms of the protein α -dystroglycan or a complete absence of the protein was associated with muscular dystrophy. But recently acquired evidence indicates that some forms of muscular dystrophy are caused not by problems with the protein per se but instead with the sugars associated with it.

"If α -dystroglycan is not properly glycosylated, then it doesn't form the complex that regulates the neuromuscular junction," Hart explained. "When that happens, your nerves don't communicate with your

muscles. It's one of the best examples in the field of glycobiology of the way sugars can regulate the function of a protein and cause human disease."

Geneticist Robert J. Desnick of Mount Sinai Medical Center, New York City, told Benzon attendees about another important class of glycan-related disorders, the lysosomal storage diseases (LSDs). Gaucher disease, Fabry disease, Pompe disease, and other LSDs are conditions in which enzymes that break down glycans for disposal are mutated or absent. The undigested biomolecules accumulate in cell lysosomes, causing neurodegeneration and other clinical problems.

In some LSDs, one or two amino acid substitutions cause a carbohydrate-degrading enzyme to misfold. Targeting such an enzyme with small-molecule drugs called "chaperones" can sometimes tweak it into a better fold and thereby enhance its activity considerably, Desnick said.

Amicus Therapeutics, in Cranbury, N.J., is trying to develop chaperones as LSD treatments. The company currently has candidate compounds in clinical trials for Gaucher disease, Fabry disease, and Pompe disease.

Many glycans express their functional roles by way of binding and molecular-recognition processes. Scientists at the biopharmaceutical firm Organon, in Oss, the Netherlands, have used carbohydrate binding and recognition to develop two commercial pentasaccharide drugs that act as anticoagulants and antithrombotics. The drugs' mechanism involves binding to antithrombin III (AT-III), a component of the blood-clotting system.

The first drug, fondaparinux (Arixtra), now marketed by GlaxoSmithKline, is a low-molecular-weight analog of a key pentasaccharide repeating unit in heparin. Heparin is a polysaccharide that has long been used clinically as an anticoagulant. Fondaparinux has greater specificity of action and fewer side effects than heparin.

Commercialized in 2002, fondaparinux was "the first synthetic low-molecular-weight heparin drug that reached the market," said Stan van Boeckel, Organon's head of medicinal chemistry. Carbohydrates are notoriously difficult to synthesize, and fondaparinux is a poster child for synthetic complexity: Making it takes 56 steps. "It is, due to its lengthy synthesis and highly rich molecular structure, the most complex synthetic drug currently available commercially," van Boeckel said.

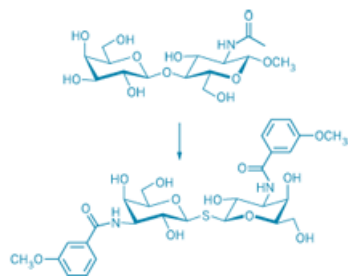
Organon researchers also developed a fondaparinux follow-up called idraparinux, which has been acquired by Sanofi-Aventis and is currently in late Phase III clinical trials. The synthesis of idraparinux is much easier than that of its predecessor, involving "only" about 28 steps. Idraparinux has higher potency and better longevity of action than fondaparinux, and its longer lifetime in the bloodstream enables it to be administered less frequently (once a week instead of once a day). Its extended duration of action is due to its strong and specific interaction with AT-III, which prevents rapid renal clearance of the agent, van Boeckel said.

Organon researchers are now using the same mechanistic concept—binding of heparin-like pentasaccharides to AT-III—to extend the useful lifetimes of other therapeutic peptides and small proteins, making it possible to administer them less frequently as well. In the company's patented CarboCarrier approach, developed by Organon bioorganic chemist Martin de Kort, peptides or proteins are conjugated with a pentasaccharide that binds AT-III.

By riding along with AT-III via the pentasaccharide intermediary, the conjugated peptides or proteins are shielded from the kidneys' drug-removal mechanisms. For example, a CarboCarrier version of insulin acts to suppress blood glucose levels just as insulin does, but its longevity of action in rats is extended by several hours relative to that of insulin, meaning that it could be administered less frequently.

GLYCAN BINDING and molecular recognition processes can also cause carbohydrate-decorated cells and microorganisms to be directed to target structures and tissues. For example, flu virus attaches to host cells via interactions between hemagglutinins (antigenic glycoproteins on the viral surface) and sialic acid residues on host cells. Potential therapeutic applications of drugs that block or promote such interactions are varied and numerous.

Structural information about the sugar-binding events that underlie viral infections "is of key importance for the rational design of viral entry inhibitors," said chemistry professor Thomas Peters of the University of Lübeck, in Germany. He and his coworkers are probing these interactions by using saturation transfer difference nuclear magnetic resonance (STD NMR) spectrometry.



Designed Potency Carbohydrates (like the one at the top) that bind galectin-3 with potencies only in the tens of μM range were redesigned into agents (like the one at the bottom) that bind the protein more than 1,000 times more potently.

With STD NMR, protons on a virus' outer shell are magnetized at an excitation frequency that doesn't affect proton resonances of most host-cell-surface glycans. The only host glycans that are affected are those in direct contact with the virus. This makes it possible to detect those glycans and analyze them structurally at atomic resolution, a level of detail that wasn't accessible with earlier techniques used to study virus-cell interactions.

STD NMR "makes insights available that five or 10 years ago were just dreams," commented Beat Ernst, a professor of molecular pharmacy at the University of Basel, in Switzerland. "It adds to the arsenal of methods available to medicinal chemists to study ligand-target interactions and can greatly support the drug discovery process."

Many other disease-causing microorganisms exploit sugar interactions to enter host cells. Chemistry professor Peter H. Seeberger and coworkers at the Swiss Federal Institute of Technology, Zurich, have found new details about the carbohydrate interactions involved when the malaria-causing parasite *Plasmodium falciparum* enters host cells.

They discovered that an interaction between a glycosyl phosphatidyl inositol (GPI) on the microorganism and a specific protein on host-cell surfaces is a prerequisite for the parasite to enter cells. *P. falciparum*'s GPI is structurally distinct from any human GPI, so Seeberger and coworkers believe it to be a good target for the development of antimalarial drugs and vaccines.

A particular glycan's biological effect is often mediated by its interaction with glycan-binding proteins known as lectins. Lectins interact selectively with sugar-containing compounds by recognizing specific glycosylation patterns. These glycan-protein interactions are of central importance to human health, and researchers are trying to manipulate them for therapeutic purposes.

But even when specific glycan-protein interactions are known to be therapeutically promising, the interactions can be difficult to exploit for drug discovery purposes. One obstacle has been the inherent weakness of most carbohydrate-protein interactions. Potencies of such interactions "generally start at the millimolar level, which is terrible, whereas most drugs have submicromolar or nanomolar potencies," Hindsgaul said. "Only recently are breakthroughs being made in how to deal with this."

FOR INSTANCE, Swedish researchers recently used parallel synthesis, screening, and structure-based design to improve the affinity of glycan ligands for a lectin called galectin-3. Interactions between galectin-3 and specific carbohydrates affect processes like apoptosis, intracellular trafficking, and cell adhesion. But galectin-3 binds relatively weakly to natural carbohydrate ligands.

Hakon Leffler, a specialist in glycan-protein interactions, and organic chemist Ulf J. Nilsson, both of Lund University, suspected that carbohydrates that bound more tightly to galectin-3 would have therapeutic potential. So they created a small library of carbohydrate variants by parallel synthesis, screened them for

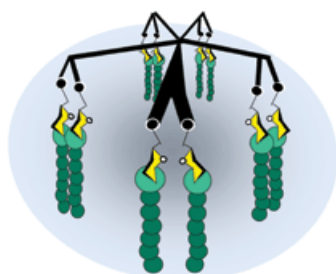
galectin-3 binding activity, and optimized their structures by rational design.

The result was a set of carbohydrate ligands with much higher binding affinities than the original compounds. One binds galectin-3 at the 50-nM level, a more than 1,000-fold improvement over the affinity of the native ligands. Initial testing in cells showed that some of the designed carbohydrates are effective at inhibiting galectin-3 and are not toxic. Leffler and Nilsson plan to scale up syntheses of the best prospects and test the agents in a mouse model of human breast cancer.

In living cells, glycans often pick up extra potency by binding to proteins in groups, that is, multivalently. Multivalent binding increases the affinity of glycan-protein interactions exponentially, and researchers can mimic that process to enhance glycan-protein binding for drug discovery purposes.

For instance, individual carbohydrate molecules interact only weakly with CD22, a lectin found on the surface of the immune system's B cells. Molecular biology professor [James C. Paulson](#) of Scripps Research Institute and coworkers recently used a clever structural assembly to get a glycan to bind CD22 multivalently. They linked one end of each glycan molecule to an antigen that binds IgM antibody. IgM antibodies are decavalent, so 10 molecules of the carbohydrate were assembled into a single complex this way.

The multivalent complex has potential therapeutic implications because CD22 is a known target for treatment of B-cell leukemias. The complex's carbohydrates can recruit IgM to CD22-bearing B cells, and the antibody can then mark the cells for destruction by other components of the immune system.



James Paulson

More is Better This complex of 10 trisaccharides (yellow rings) and 10 antigen molecules (black circles) with an IgM antibody (black umbrellalike structure) binds the lectin CD22 (segmented green chains) multivalently. The immune complex could be used to mark CD22-bearing leukemic cells for destruction.

Decavalency may not always be possible to attain, but sometimes even divalency is effective at enhancing interactions. Ernst and his coworkers recently used a novel approach to create a divalent agent that interferes with a problematic interaction between myelin-associated glycoprotein (MAG) and neuronal gangliosides (sialic acid-containing glycolipids). This interaction can inhibit axonal regrowth after neuronal injury, so the researchers believe an interfering agent might promote healing after such injuries.

In a fragment-based design approach, Ernst and coworkers used NMR to find two adjacent sites on MAG at which the glycoprotein binds different gangliosides. They then identified two compounds that each bound one of those sites and combined them.

The result was a glycan-like divalent agent with high binding affinity for MAG. The agent binds the glycoprotein with a nanomolar dissociation constant, a nearly 1,000-fold improvement over the more potent of the two monovalent compounds.

Such agents have potential therapeutic applications. The MAG-ganglioside interaction is one of several processes that can inhibit axon regeneration and "limit recovery from central nervous system injury and disease," Ernst said. "Molecules that block such interactions may enhance axon regeneration and functional recovery."

Neuroglycobiologist [Ronald L. Schnaar](#) and coworkers at Johns Hopkins University School of Medicine have also been focusing on MAG interactions. They wanted to find a way to interfere with an interaction between MAG and a neuronal ganglioside, another interaction that inhibits nerve regeneration.

Schnaar's group has found that treating animals with the enzyme sialidase induces axon regeneration and promotes functional recovery after traumatic nerve injury. Sialidase removes a terminal sialic acid from MAG-binding gangliosides, interfering with the interaction. Although the side effects of such a treatment are currently unknown, the approach suggests the potential of using carbohydrate-active enzymes as drugs.

Other researchers at the Benzon Symposium noted that it's often useful to change the way biomolecules and other compounds are glycosylated to create novel agents with therapeutically valuable biological activities. That strategy has been adopted, for example, by professor [Jon S. Thorson](#) of the University of Wisconsin School of Pharmacy, Madison, and coworkers, who have developed an approach for rapidly synthesizing libraries of glycosylation variants.

THEIR TECHNIQUE, called neoglycorandomization, uses a series of chemical reactions to quickly add a variety of different sugars to compounds. The resulting glycosylation variants can then be tested against specific targets for their affinity and selectivity. An earlier version of the technique, called glycorandomization, relied on enzymes instead of chemical steps to glycosylate compounds, but it wasn't as efficient as neoglycorandomization.

Thorson and coworkers recently used neoglycorandomization to improve the potency of the antibiotic vancomycin by replacing its disaccharide group with glucose-lipid substituents (*J. Am. Chem. Soc.* **2007**, *129*, 8150). "Neoglycorandomization is an exceptionally useful approach that opens a totally new avenue for drug discovery," Ernst commented.

Thorson's group has also made progress toward an in vivo version of glycorandomization. The idea would be to feed different compounds and sugars to a microorganism, which would then do the heavy lifting to combine them into glycosylation variants. Thorson noted that "the entire glycorandomization and neoglycorandomization technology platform, as well as a number of our advanced leads, has been licensed to Centrose," a Madison-based company he founded.

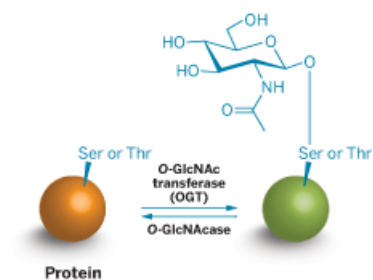
Glycosylation changes can be used to modify medicinal properties not only of individual compounds but also of whole cells. Assistant professor of medicine [Karin Hoffmeister](#) and coworkers at Brigham & Women's Hospital, Boston, in collaboration with Clausen's group, discovered that modifying glycans on the surface of blood platelets enables the cells to be refrigerated and stored for a longer time than is currently possible.

Platelets are used therapeutically to stop bleeding. They currently must be stored at room temperature and can be kept only about five days before bacterial contamination becomes a problem. Refrigerating them could preserve them longer, but patients' bodies eliminate refrigerated platelets almost immediately.

It's a problem that Hoffmeister and coworkers have been able to detail on the molecular level and now hope to overcome. They discovered that macrophages devour platelets when they recognize clusters of *O*- β -*N*-acetylglucosamine (*O*-GlcNAc) groups on platelet surfaces. *O*-GlcNAc clumps together in this way only when platelets are cooled for hours.

The researchers have been trying to shield the clumped *O*-GlcNAc groups from macrophage scrutiny by galactosylating or sialylating them. These modifications occur spontaneously when the scientists add reactive forms of galactose and sialic acid to platelets, because the cells themselves possess the glycosylation enzymes needed to make the reactions go.

The galactosylation approach worked in mice given treated platelets, but in a recent human clinical trial, galactosylation proved ineffective at preventing clearance of platelets that had been refrigerated for 48 hours. "Adding galactose promotes another platelet clearance mechanism," Hoffmeister concluded. "Sialylation is the next logical step," a clinical trial of which "will be performed in the near future," she said. Also, [ZymeQuest](#), of Beverly, Mass., has licensed the *O*-GlcNAc-shielding approach and is trying to develop it.



Ser = serine, Thr = threonine, O-GlcNAc =
O-linked β -*N*-acetylglucosamine

Gerald Hart

More is Better O-GlcNAc is added to proteins by one enzyme and taken off by another. The carbohydrate plays a key role in cell signaling, transcription control, and other functions.

The work shows that carbohydrates "are not just decorations but have a real impact on health care," Ernst said. Masking O-GlcNAcs on platelets "could be instantly important in solving a serious medical problem."

Hart noted that increased GlcNAcylation—glycosylation with O-GlcNAc, a process his group discovered in 1984—promotes insulin resistance, a hallmark of diabetes, and that it helps protect cells from stress, inhibits protein degradation, and can either boost or curb gene transcription. GlcNAcylation thus has a wide range of physiological effects on cells, and errors in GlcNAcylation are associated with neurodegenerative diseases, diabetic glucose toxicity, cancer, and other conditions.

"The ubiquitous roles of GlcNAcylation in signaling, transcription, and cytoskeletal functions are an unexplored avenue for drug discovery," Hart said. Monsanto and other companies once had programs to develop inhibitors of O-GlcNAc transferase, the enzyme that catalyzes GlcNAcylation, he said, "but many of these were dropped." In part, this is because O-GlcNAc transferase is so essential, raising fears that inhibiting it could cause serious side effects, he said.

But targeting drugs to specific O-GlcNAc transferase interactions in a highly selective manner might reduce the potential for side effects, Hart said. For example, he noted, inhibiting an O-GlcNAc transferase interaction with a specific nuclear receptor activator might lower inappropriately high glucose levels in diabetics without affecting normal GlcNAcylation.

Changes in the branching structure of cell-surface oligosaccharides can also have a big impact on human health and disease. An improved understanding of these molecular nuances could lead to new types of therapeutics for cancer, diabetes, autoimmune diseases, and other conditions, researchers pointed out at the symposium.

Two groups—a team led by professor James W. Dennis of Mount Sinai Hospital, Toronto, and Pierce's University of Georgia group—have found independently that the level of complexity of the branching structure of cell-surface glycoprotein receptors helps regulate cell signaling and can profoundly influence cell function. For example, if the degree of branching of carbohydrates on surfaces of cancer-forming cells is reduced, the cells don't proliferate or spread as much. This suggests that inhibiting cell-surface glycosylating enzymes might have anticancer activity.

GLYCAN CENTRAL

Shared Resource Seeks Its Continuance

A shared resource that in the past few years has become increasingly essential to scientists studying the complex dynamics of protein-glycan interactions is the Consortium for Functional Glycomics (CFG), directed by molecular biologist James C. Paulson of Scripps Research Institute. Glycans are complex sugar structures found in, on, and around cells.

CFG's government funding will soon come to an end, after which it will need to find a way to survive independently. Paulson discussed the consortium at last month's Benzon Symposium on Glycosylation, in Copenhagen.

Researchers affiliated with CFG study glycan-protein interactions and the way these interactions influence and control cell functions. The consortium's most popular tool for studying such interactions is the glycan array, which is a small surface covered by hundreds of different glycan structures. The scientists use it to screen carbohydrate-binding proteins and identify the carbohydrate ligands with which they interact.

"The consortium produces these arrays, and they're available to everybody for free," said chemistry professor Ole Hindsgaul of Carlsberg Laboratory, Copenhagen, an organizer of the symposium. "You don't even have to do the screening experiments. Consortium scientists do them for you," he said.

"The rule is that you use consortium resources for free, but you have to post your results on their website within six weeks," Hindsgaul pointed out. "That gives you time to file for patents on carbohydrate-binding proteins if you need to do that. The findings must be made public because they're paid for by public money."

The consortium was established in 2001 with a five-year "glue grant" from the National Institute of General Medical Sciences (NIGMS)—a funding mechanism used to start up new shared scientific resources. CFG is now on its second five-year glue grant. Together, the two grants have amounted to \$75 million.

Glue grant funding lasts only up to 10 years, so CFG will need to find new funding beginning in 2011. "NIGMS is being very proactive in identifying the aspects of CFG that need to be continued," Paulson said. The institute "will be working with us to ensure that valuable resources currently available to the community will continue after the glue grant funding has expired."

The mechanism of such effects appears to involve changes in glycoprotein residence time on cell surfaces. Highly branched cell-surface glycans have a greater tendency to bind to lectins. These interactions create a molecular network, or lattice, that causes the receptors to stay on the surface. However, if glycan branches are missing, glycan-lectin binding interactions loosen. This permits the glycoprotein receptors to leave the cell surface and become sequestered in vesicles inside the cell, where they become inactive.

"THESE RECEPTORS must be retained on the surface for a proper length of time so they can do their jobs," commented cell biology professor Pamela Stanley of Albert Einstein College of Medicine, New York City, a session chair at the symposium. Their removal from the surface "inhibits growth factor signaling, which is mediated by those cell-surface glycoproteins," she said.

Glycoimmunology specialist Jamey D. Marth of Howard Hughes Medical Institute at the University of California, San Diego, and coworkers have found that reductions in oligosaccharide branching and the consequent loss of cell-surface carbohydrates can also cause a diabetes-like disorder. They discovered that a particular glycosyltransferase enzyme must be active for a glucose transporter glycoprotein to stay on the surface of pancreatic β cells, the cells that manage blood glucose levels.

When expression of this glycosyltransferase is knocked out in mouse pancreatic β cells, glycosylation of the glucose transporter is reduced, its branching becomes less complex, and the glycoprotein is not retained on the cell surface. This causes a glucose-transport deficiency that makes the cells unresponsive to glucose

and unable to secrete insulin when they should, thereby causing a diabetes-like condition. Marth and coworkers found that high-fat diets also knock down the enzyme's expression, showing how such diets might lead to diabetes.

Marth's group also recently demonstrated a way in which cell-surface glycans can act as immune indicators of self or nonself. The researchers found that reduced α -mannosidase-II activity changes the composition of vertebrate cell-surface glycans, favoring the incorporation of mannose at the expense of other sugars. The resulting high-mannose glycans resemble foreign (microbial or invertebrate) cell-surface glycans and can therefore elicit an immune response or cause an autoimmune disease like lupus.

The mammalian forms of cell-surface glycans "keep us from looking like microbes and other organisms," Marth said. "Should we don the wrong glycan cloak, one that mimics these organisms, autoimmune disease can develop as our body tries to fight itself. It is a novel mechanism of autoimmune disease."

Research on rheumatoid arthritis, another autoimmune disease, reveals that carbohydrate recognition may play an important role there as well. Inflammation specialist [Rikard Holmdahl](#) of Lund University and coworkers found that rheumatoid arthritis can be induced in mice by injecting them with collagen with modified glycosylation patterns. Immune system T cells in the mice recognize the glycosylation variations, causing the autoimmune condition. Human rheumatoid arthritis patients were sensitive to collagen with the same types of glycosylation changes, suggesting that such structures could be starting points for the development of rheumatoid arthritis vaccines.

In the future, the number of such glycan-focused drug targets is likely to grow considerably. "Probably when we look at carbohydrate-based drug discovery 10 years from now, we will smile about our efforts, just as we smile today about those from 10 years ago," Ernst said. "A number of carbohydrate-based drugs are now on the market, and the field is just exploding in all directions. It's more and more fascinating. When you list all the therapeutic possibilities you can think of with carbohydrate-based drugs, it's absolutely endless."

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