Glycosylation Engineering

Controlling personalities tame wild sugars on proteins and natural products

Stu Borman
SUGARS ARE KEY Sugars (orange) in the aryltetrasaccharide part of the antitumor natural product calicheamicin (white and yellow) play a key role in the agent's ability to recognize and bind to the calicheamicin self-sacrifice protein, CalC (blue region and green ribbon). Thorson and coworkers, in collaboration with UW Madison's Center for Eukaryotic Structural Genomics, recently solved the structure of the calicheamicin-CalC complex, revealing the essential nature of the aryltetrasaccharide-protein interaction (ACS Chem. Biol. 2006, 1, 451). The importance of sugars in such interactions has helped spark efforts to modify and better control them.

Carbohydrate chemists and biochemists tend to be controlling personalities. They aren't satisfied with the way sugar groups are attached naturally to glycosylated proteins and natural products. These scientific drill sergeants think they can do better. So they're busy most days devising new ways to whip fractious glycosylated biomolecules into shape. And these control freaks are actually making remarkable progress at achieving their desired results.

So how does one control the glycosylation of a protein or natural product these days? Let us count the ways.

It can be done by the bioengineering of bacteria, yeast, plant cells, insect cells, and mammalian cells. Those are five ways right there. It's done by manipulating protein or natural product glycosylation pathways in genetically engineered organisms. Compounds also can be glycosylated by exploiting the liberality with which sugar-attaching enzymes (glycosyltransferases) tolerate a wide range of different substrates. That's two more ways. And one can glycosylate proteins and natural products through a variety of chemical approaches: with enzymes, protein ligation, metabolic bioengineering, or total synthesis. That's 11 ways to modify carbohydrate groups in need of a little taming.
More than 50% of human proteins are glycoproteins, which tend to be heterogeneously glycosylated. That means the structures of attached sugars and the sites to which they're attached are variable. A wide range of bioactive natural products are glycosylated as well, including anthracycline antitumor antibiotics, avermectin antiparasitics, enediyne antibiotics, macrolides such as erythromycin, and glycopeptide natural products like vancomycin. Some natural products are also heterogeneously glycosylated, although generally to a lesser degree than glycoproteins.

Whether glycoproteins and glycosylated natural products are heterogeneously glycosylated or not, researchers have felt the need to better control which sugars go where on these molecules. The idea is to improve on Mother Nature because sugars are often essential to the functions of biomolecules, and the ability to modify and control which ones are attached and exactly how they're attached can make it possible to tailor biomolecular structure, folding, stability, immunogenicity, uptake, distribution, target recognition, and other properties and functions of these compounds.

For example, glycosylated biomolecules can be turned into better drugs by manipulating their sugars. Appropriate glycosylation of erythropoietin (EPO), an approved glycoprotein drug for anemia and cancer, is critical for its activity and longevity of action, and its properties have been improved by modifying its glycosylation through genetic engineering. Researchers would like to be able to totally control the glycosylation of drugs like EPO. But EPO and most other glycoprotein drugs are currently produced commercially in mammalian cells, which express them as mixtures of different glycoforms (versions with variable glycosylation), and this is a hard process to control.

"Glycosylation is a very complicated pathway," with mammalian cells typically using hundreds of enzymes to glycosylate proteins, says Markus Aebi, a specialist in microbial glycobiology at the Swiss Federal Institute of Technology, Zurich. "So it's difficult to generate glycoproteins that have a defined structure at a defined point in the protein" by producing them in mammalian cells.

Aebi and coworkers have devised effective ways to make homogeneously glycosylated proteins in bioengineered prokaryotes. They focus primarily on glycosylation involving N-glycans, in which sugars are linked to proteins via asparagine residues, because that is the predominant type in human glycoproteins.

N-glycosylation was originally believed to be a purely eukaryotic process. But it is now possible to bioengineer bacteria to make proteins functionalized with N-glycans. "We are not at the stage where we reconstruct human sugar structures in E. coli," Aebi says, but bacteria can now be made to put simpler sugars on asparagine residues, as human cells do.

Aebi and coworkers initiated bacterial N-glycosylation in 2002, when they found an unusual N-linked glycosylation system in the pathogenic bacterium Campylobacter jejuni, transferred it into Escherichia coli (which is much easier to manipulate genetically), and used the transplanted system to generate N-glycoproteins. They have now elucidated the substrate specificity and mechanism of the key enzyme of that system, and these findings may help them design bacteria that can produce glycoproteins with a greater variety of sugars.

One advantage of bacterial bioengineering is that bacteria aren't very sensitive to glycosylation
changes. "In E. coli, you can do whatever you want," Aebi says. "They usually don't care," whereas eukaryotic cells can die if you manipulate their glycosylation systems too much.

Another way of using bacteria to create glycoproteins with customized glycosylation was devised in 2004 by Peter G. Schultz, director of the Genomics Institute of the Novartis Research Foundation, La Jolla, Calif.; chemistry professor Chi-Huey Wong of Scripps Research Institute; and coworkers. They engineered bacteria to take up N-acetylglucosamine (GlcNAc) or N-acetylgalactosamine (GalNAc) derivatives of amino acids. The sugars then are incorporated as the protein is made in the ribosome rather than being added to the protein after it comes out of the ribosome, as happens in nature or in conventional bacterial bioengineering.

So far, the most commercially successful cellular system for glycosylation bioengineering is yeast. Yeast can make lots of glycosylated protein at fairly low cost. But yeast sugars, like those in bacteria, don't look anything like human sugars. "That's a problem for glycoprotein biotherapeutics because if the sugars don't look like human sugars, they're not going to have the properties you'd like," says chemistry professor Carolyn R. Bertozzi of the University of California, Berkeley. Yeast sugars are also "weird-looking to the human immune system, so humans could mount an immune response against them," she says.

Researchers have sidestepped this problem by genetically engineering yeast to express glycosyltransferases and substrate-producing enzymes imported from other organisms. But to do so, one first has to eliminate interfering native-yeast versions of the enzymes to be introduced, which is tricky.

"You are limited in what you can do because glycosylation is an essential process that yeast cells need to make a living," Aebi says. "If you change it too much, you kill the cells."

The group of associate professor of engineering Tillman U. Gerngross at Dartmouth College and researchers at GlycoFi, Lebanon, N.H., a company he cofounded, have been notably successful at making the generation of humanlike glycoproteins by yeast a reality. In May, Merck announced that it was acquiring 100% of the equity of GlycoFi for about $400 million.

GLYCOYEAST At GlycoFi, process engineer Adam Sharkey (left) harvests shake flasks in which humanized yeast is used to make therapeutic proteins, and process engineer Gavin Barnard checks
mini-fermenters in which humanized yeast is screened.

"Yeast is a proven platform in which people have been making proteins; half the world's supply of insulin, a product made in metric-ton quantities, is made in yeast," Gerngross says. "Yet yeast was relegated to the production of proteins like insulin, which are not glycosylated."

Gerngross and coworkers believed that if they could get yeast to glycosylate in a human way, they would be able to take advantage of the microorganism's favorable process economics to produce designed glycoproteins. "We ended up executing that in fairly deliberate fashion and have been able to 'humanize' yeast entirely," Gerngross says. That means they can use yeast to produce glycoproteins with complex biantennary (two-branch) N-glycans, like those in human glycoproteins—except that the glycoproteins are homogeneously glycosylated, unlike those in humans.

Homogeneously glycosylated humanlike glycoproteins produced in yeast can be used to study the effects of different forms of glycosylation on glycoprotein therapeutic activity. Gerngross and coworkers recently showed that a homogeneously N-glycosylated form of the therapeutic antibody rituximab is at least an order of magnitude more active in binding its target receptor than the current commercial drug (Nat. Biotechnol. 2006, 24, 210).

Such a study would be difficult to carry out with mammalian cells, which tend to generate "10 or 15 different glycoforms all mixed together," Gerngross says. "Using that convoluted system to figure out which glycoform gives you more activity is very difficult, if not impossible."

Gerngross says he believes the combination of Merck's expertise in yeast expression and GlycoFi's in glycoengineering "will produce critical candidates across a broad spectrum of different indications and molecule classes. It could be vaccines, antibodies, or serum-type proteins like EPO and interferons—all these can now be produced in yeast with very homogeneous human glycosylation with optimized glycoforms, and that was formerly not possible in any system."

Plant cells can also be used for glycosylation engineering, but the technology is at a distinctly earlier stage of development than that for yeast cells. Compared with bacteria and yeast, plant cells can synthesize humanlike complex N-glycans with fewer manipulations needed; however, glycoproteins produced by unmodified plant cells have specific xylose and fucose residues that tend to be immunogenic. Therefore, "relatively laborious and time-consuming transformation and regeneration procedures are necessary to genetically manipulate plants" to eliminate the possibility that problematic residues will be added by their glycoprotein production systems, says associate professor of plant molecular biology Herta Steinkellner of the University of Agricultural Sciences, Vienna.

On the other hand, plants can be engineered to eliminate potentially immunogenic fucose and xylose sugars from their glycoproteins, according to a 2004 study by assistant professor of molecular plant biotechnology Richard Strasser of the University of Agricultural Sciences and coworkers, including Steinkellner.
Plant cells have another complication. They don't make galactose because they lack a key enzyme, and this sugar has to be added to plant N-glycans to make them more humanlike. A major step toward addressing that complication, achieved about five years ago by two independent groups, was the genetic engineering of plants to express galactosyltransferase, which adds galactose to glycoproteins.

**HUMANIZATION**

Simplified version of a strategy developed by Betenbaugh and coworkers for humanizing glycoproteins produced in insect cells. The cells are genetically engineered to express metabolic enzymes and glycosyltransferases needed to add sialic acid, galactose, and N-acetylglucosamine residues to insect glycans (left).

Sialic acid is another amino acid that characterizes human glycoproteins but is missing in plants. Several groups are now trying to introduce a sialic acid pathway into plants, "with limited success so far," Steinkellner says. The problem is that adding sialic acid groups to glycoproteins requires the addition to plants of genes for up to seven different enzymes and other proteins, and this is quite difficult.

Glycoproteins can also be made in insect cells. The sugars produced naturally in insect cells also look more like human ones than those produced naturally in bacteria and yeast. "Insect cells represent a good starting point for glycoengineering modifications," says professor of chemical and biomolecular engineering [Michael J. Betenbaugh](http://pubs.acs.org/cen/coverstory/84/8436glycosylation.html) of Johns Hopkins University. Nevertheless,
a significant number of genes must be added to insect cells to achieve fully human glycosylation. Required modifications include the expression of missing glycosyltransferases and the addition of key glycosylation-tweaking metabolic enzymes.

For example, insect cells lack significant galactosyltransferase activity. But Betenbaugh's group and professor of molecular biology Don Jarvis of the University of Wyoming and coworkers have independently created bioengineered insect cells that produce N-glycans with full galactosylation on both branches of biantennary N-glycans.

The absence of sialyltransferase activity in most insect cells is another roadblock that appears to have been overcome. Betenbaugh's group, in collaboration with Johns Hopkins biology professor Yuan Chuan Lee and coworkers, has reconstructed the metabolic pathways required for sialylating glycoproteins. And Jarvis' group has bioengineered this metabolic system into insect cells and has obtained the first fully sialylated and completely humanized glycoproteins from such cells. "The general advantages of our modified insect systems include the ability to provide reasonably high levels of recombinant glycoprotein production with authentic N-glycans relatively quickly, at relatively low cost, and in a biologically safe system," Jarvis says.

Ultimately, the best type of cell in which to express humanlike proteins without the need for a lot of rejiggering would be human cells, or at least mammalian ones. The problem is that mammalian cells tend to be very unproductive and quite expensive. "It's hard to get a lot of material, and it costs a fortune," Bertozzi says.

But the practicality of mammalian-cell glycoengineering has been improving. Researchers at Amgen recently used engineered mammalian cells to insert modified N-glycans into therapeutic proteins like EPO. The modifications increased the drugs' activity and prolonged their duration of action, thereby reducing the frequency with which they might need to be administered.

Efforts to glycoengineer mammalian cells are also being carried out at Zurich-based GlycArt Biotechnology, a member of the Roche group. Chief Scientific Officer Pablo Umaña and coworkers glycoengineer mammalian cells to modify the drug properties of therapeutic monoclonal antibodies (mAbs), such as those targeting cancer. When anticancer mAbs are injected into patients, they home in on tumor cells. When the tumor-bound mAbs then bind to receptors on immune system cells, they cause an immune reaction against the cancer. These binding interactions are mediated by sugars. Umaña and coworkers enhance the interactions by modifying sugars. For example, when they modify antibody glycosylation to eliminate fucose, the interaction is generally about 50 times stronger than when fucose is present.
**MODIFIED** Modified Umaña and coworkers modify the glycosylation (stick structure) of the Fc region of antibodies such as this tumor-cell targeting antibody (space-filling representation) to enhance their binding affinity to receptors on recruited immune cells.

To make this kind of modification, Umaña and coworkers introduce into mammalian cells a plasmid vector (small piece of DNA) that codes for a mAb and another that codes for glycosylation enzymes that compete with endogenous mammalian fucosyltransferase. When the mAb is produced and goes through the secretion apparatus of the cell, where glycosylation occurs, it acquires a modified sugar pattern lacking fucose. Independently, researchers at Kyowa Hakko Kogyo, Tokyo, have created mammalian cells in which a fucosyltransferase gene has been knocked out to do the same kind of thing.

Umaña's group has generated mammalian cell lines that produce 3 to 5 g/L of fucose-deficient antibody in two weeks, a productivity that is in the upper range of levels obtained with nonglycoengineered mammalian cells. One of these glycoengineered therapeutic antibodies is now in clinical trials, and Umaña hopes others will be soon. "It's an exciting time," he says.

As they do with proteins, attached sugars affect the bioactivity of a wide variety of natural-product-based drugs, and natural products are thus another major target of glycoengineering efforts. One approach that has attracted considerable attention is combinatorial biosynthesis, the randomized genetic engineering of "cassettes" of microbial enzymes that biosynthesize natural products in an assembly-line process. Because of the modular nature of these cassettes, enzyme components can be modified to render them capable of producing glycosylation variants.

Professor of biology José Salas and coworkers at the University of Oviedo, Spain, use a different
tack. They insert into microorganisms plasmids that endow them with the ability to synthesize novel sugars, which are then transferred to natural products by glycosyltransferases. "Because glycosyltransferases are relatively flexible in their ability to recognize and transfer different sugars, the final result is the generation of novel glycosylated derivatives from a natural product that the microorganism usually synthesizes," Salas says.

Salas and coworkers recently generated glycosylated derivatives of the protein-kinase inhibitor staurosporine this way and are testing them for inhibitory potency. This technology is also being used by EntreChem, a University of Oviedo spin-off company they founded, to produce anticancer drug candidates.

A plethora of chemistry-based approaches has also been developed for controlling glycosylation of proteins and natural products outside of bioengineered cells and organisms. Several of these techniques use enzymes or previously bioengineered proteins as synthetic reagents and are therefore sometimes called "semisynthetic."

One way to use enzymes semisynthetically is to first use bioengineering to express a protein bearing a core sugar like GlcNAc or GalNAc, to which other sugars can be added. "You don't need a big polysaccharide, just a starting point," Bertozzi says. "One can purify the derivatized protein, and then in a test tube use enzymes to build up more complex structures" by adding additional sugars to the core unit.

On another front, chemistry-based methods are exploiting a peculiar characteristic of glycosyltransferases: their promiscuity, or tolerance for substrate variation. So by simply varying the substrate, a large number of carbohydrate analogs of natural products can be made.

For example, professor of pharmaceutical sciences Jon S. Thorson and coworkers at the University of Wisconsin, Madison, have exploited glycosyltransferase promiscuity in glycorandomization, a method they use to attach varied sugars to natural products. In this technique, engineered enzymes are first used to convert monosaccharide libraries to sugar nucleotides, an activated form of the sugars. The sugar nucleotides then serve as substrates for promiscuous glycosyltransferases, which attach the sugars to natural products or natural-product-like compounds. The resulting glycorandomized libraries can then be screened for interesting types of bioactivity.

Glycorandomization can be carried out in vivo by expressing glycosyltransferases and other key enzymes in bacteria. But most glycorandomization has been done outside living systems.

"We have glycorandomized a number of natural products in the past year," Thorson says. Examples include the synthesis of about 30 macrolide analogs (in collaboration with chemistry professor Hung-wen Liu of the University of Texas, Austin), more than 50 analogs of antiparasitic avermectins, and more than 70 variants of the anticancer agent calicheamicin.
ENHANCED Binding interaction between the Fc (constant) region of a glycoengineered antibody (red and blue) and a receptor on a recruited immune cell (green), a key asparagine of which is yellow. The carbohydrate (stick structure), modified by Umaña and coworkers, enhances the antibody’s binding affinity for the receptor, compared with that of an unmodified native antibody.

Thorson and coworkers recently developed a simplified version of glycorandomization called neoglycorandomization, in which sugar ligations are carried out chemically, without any need for either prior sugar activation or enzymes. They used that method to convert the heart drug digitoxin into analogs with anticancer activity, some of which are being tested in mouse cancer models, and to convert colchicines, which are tubulin destabilizers, into analogs with tubulin stabilizer activity (C&EN, Aug. 15, 2005, page 7).

Most recently, they made a discovery about the reversibility of glycosyltransferase-catalyzed reactions that allows them to transfer sugars directly from one natural product to another (Science 2006, 313, 1291). Glycosyltransferases have generally been thought of as unidirectional enzymes that catalyze glycosidic bond formation. There were hints of reversibility in glycosyltransferase-catalyzed reactions before, but the new study now clearly reveals this to be a universal phenomenon.

The researchers demonstrated the technique by using glycosyltransferases to catalyze the replacement of native sugars on natural products with exotic sugars from other natural products.
They also used it for the one-step generation of exotic sugar nucleotides, a process that requires up to 10 steps by classical chemical synthesis.

Thorson recently cofounded Centrose, a Madison-based company focused on the development and commercialization of glycorandomization and the use of high-throughput screening to discover new therapeutic leads.

Efforts to semisynthetically manipulate proteins’ sugar decorations are also ongoing at Neose Technologies in Horsham, Pa. Researchers there use enzymes to remodel and optimize recombinant glycoproteins after their expression to enhance their properties, a process they trade-named GlycoAdvance. For example, they used a sialyltransferase and a fucosyltransferase to add sialyl Lewis X to N-glycans on soluble human complement receptor type 1 (sCR1) after it was expressed in mammalian cells. sCR1 is a glycoprotein being evaluated as a blood disease agent. The modifications resulted in a product that, compared with the unmodified glycoprotein, had less heterogeneous glycosylation, better pharmacokinetics, and enhanced target binding.

Yet another enzymatic glycosylation option was introduced last year by associate professor of chemistry Lai-Xi Wang and coworkers at the Institute of Human Virology and the University of Maryland Biotechnology Institute, Baltimore. Their endoglycosidase-catalyzed protein glycosylation method uses oligosaccharide oxazolines as carbohydrate donor reagents. The technique eases the synthesis of complex glycopeptides carrying multiple N-glycans, as exemplified by the group’s use of it to assemble large and complex HIV-1 glycopeptides as candidate HIV vaccines. Recently, they further simplified and extended the method, making it more efficient and permitting greater homogeneity of glycoprotein products (Org. Lett. 2006, 8, 3081). "We expect that this chemoenzymatic approach will find broad applications for the synthesis and glycosylation remodeling of therapeutic glycoproteins such as EPO and other glycoprotein hormones," Wang says.

Another semisynthetic variation is to engineer cell metabolic pathways so that cells express protein derivatives with chemically reactive sites to which sugars can then be added chemically. For instance, Bertozzi and coworkers have engineered the metabolic machinery of cells to express N- and O-linked glycoproteins labeled at specific sites with azide groups. They then use the azides to carry out coupling reactions that add new sugars to the glycoproteins.

Chemical syntheses and semisyntheses of glycoproteins can also be carried out through chemical ligation. In this approach, glycopeptide fragments with attached N-glycans are first synthesized or biosynthesized as building blocks. Then the fragments are joined chemically into full-size glycoproteins.

Ligation is used primarily because synthesizing large proteins or glycoproteins as a single unit is extraordinarily difficult. "A lot of people think that even if you can make a large glycoprotein by total chemical synthesis from scratch, it would be so cost prohibitive and the quantities of product would be so small that it would be of no practical significance," Bertozzi says. Making two or more separate glycopeptide segments and then ligating them eases the task.

Problems with ligation are that steric hindrance caused by bulky N-glycans on glycopeptide fragments can lead to low ligation yields and that the amino acid cysteine must be present at each ligation site, which is not always possible or convenient. But an advantage of ligation is that
"chemists can have complete control over the position, quantity, and type of glycosylation present in the desired target," says research fellow Derek Macmillan of University College London. Such control is not always possible when expressing glycoproteins in engineered cells, where glycosylation often tends to be heterogeneous, he notes.

Macmillan and coworkers, Wong's group, and that of chemistry professor Samuel J. Danishefsky at Memorial Sloan-Kettering Cancer Center and Columbia University have synthesized glycoproteins through chemical ligation and in some cases with versions of the technique that aren't constrained by the need for a cysteine at ligation sites. Wong and coworkers recently developed a cysteine-free technique called sugar-assisted glycopeptide ligation for such syntheses (J. Am. Chem. Soc. 2006, 128, 5626). And Danishefsky's team recently modified a cysteine-free ligation method introduced earlier by associate professor of cell biology and chemistry Philip E. Dawson of Scripps Research Institute and coworkers and optimized it for use on large glycopeptides.

Central to the Danishefsky group's approach was a new synthetic strategy: an O-to-S acyl migration reaction that sets the stage for cysteine or cysteine-free ligations and makes it possible to generate highly complex glycopeptides. They recently used this technique to help create some of the largest and most complex homogeneous EPO-like glycopeptides ever made by total chemical synthesis (Angew. Chem. Int. Ed. 2006, 45, 4116; C&EN, June 5, page 64).

Another form of chemical ligation that can be used for glycoprotein synthesis is traceless Staudinger ligation, the reaction of an azide and a phosphinothioester to form an amide. The reaction was developed independently in 2000 by Bertozzi's group and a team led by professors of chemistry and biochemistry Laura Kiessling and Ron Raines of the University of Wisconsin, Madison. Bertozzi and coworkers used metabolic engineering and traceless Staudinger ligation to put azide groups on cell surfaces, making it possible to use the azide groups as chemical handles to perform reactions on those surfaces.

This year, Wong and coworkers extended traceless Staudinger ligation to the coupling of glycopeptides, and they developed a protease-catalyzed peptide condensation method for selectively introducing N-terminal azides to peptides (ChemBioChem 2006, 7, 429). "The combined approach could be used to synthesize glycoproteins from a long, expressed polypeptide and a short, synthetic glycopeptide in a cost-efficient way," Wong and coworkers note.

Another chemical approach for synthesizing compounds with tailored carbohydrates involves the use of computer-based automated carbohydrate synthesis techniques, such as the programmable one-pot synthesis approach developed by Wong and coworkers. They used the technique, for example, to systematically modify the sugar domain of the antibiotic vancomycin in an effort to create novel antibiotics.

In parallel with efforts to find better ways to engineer and synthesize glycoproteins and glycosylated natural products, improvements are needed in the ability to analyze what's been made. Such analyses are "no trivial thing," Bertozzi says. "A handful of groups can do this, and that's it. We need better tools that allow us to quickly ask questions like, 'Under these conditions, what glycoproteins are produced, where are they glycosylated, and to what extent?' "

http://pubs.acs.org/cen/coverstory/84/8436glycosylation.html?print
One group endeavoring to provide such tools on a research scale is that of associate professor of chemistry and chemical engineering Linda C. Hsieh-Wilson of California Institute of Technology. She and coworkers study O-GlcNAc glycosylation of transcription factors unique to the brain, and her group has worked out some advanced glycoanalytical techniques for determining glycosylation sites and the structures of sugars on glycoproteins.

Effective glycosylation measurement and control systems are also needed industrially by companies that produce cell-based carbohydrate therapeutics. "Glycosylation can be extremely complex and can vary significantly depending on cell culture conditions, the state of cells, and the product workup," says Daryl Fernandes, chief executive of Ludger Ltd., Abingdon, England. "Fortunately, glycoanalytical tools and our knowledge of glycosylation in production systems are maturing, allowing biologics companies to design and manufacture safer and more effective glycoprotein therapeutics."

Overall, the field of protein and natural product glycosylation "is in really good shape," Bertozzi says. "The field of genomics has made it possible for us to sequence microbial genomes efficiently, if they're not already sequenced. From there, we can find glycosyltransferase genes and other genes that will do what we want them to do."

The availability of such genomic information helped make it possible for GlycoFi scientists to carry out glycosylation engineering so successfully in yeast, she says. "They were able to pull out glycosyltransferase genes from many different organisms and then mix and match them to get combinations that would work in yeast, and you can only do that if you have access to genomic information. That's very powerful."

In terms of applications of glycoengineered glycoproteins, the fastest growing category of therapeutic glycosylated biomolecules is mAbs."Companies like Amgen, Biogen Idec, and Genentech have to pay attention to glycosylation of those mAbs," Bertozzi says. "That means that growth in the mAb sector is going to be accompanied by growth in the biopharmaceutical industry's glycobiology sector. People who can manipulate biosynthetic enzymes, who can engineer cells to glycosylate on command, and who can synthesize glycosylated compounds in various ways can contribute a lot to glycoengineering of these recombinant therapeutics. So it's good times."

Which just goes to show that being a controlling personality is not necessarily a terrible thing.
COURTESY OF LAI-XI WANG

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