Venter Institute Team Builds *M. genitalium* Genome from Scratch

Using off-the-shelf chemicals, a team of 17 scientists at the J. Craig Venter Institute (JCVI) in Rockville Md., designed, synthesized, and assembled a small but complete bacterial chromosome—the 582,970-bp genome of *Mycoplasma genitalium* JCVI-1.0. This DNA construct, more than an order of magnitude larger than any previously reported synthetic genome, is a big step toward building fully synthetic microorganisms. Details appear in the 24 January 2008 issue of *Science*.

“The actual synthesis and assembly of this genome presented a formidable technical challenge because as strands of DNA get longer they get increasingly brittle,” says Daniel Gibson of JCVI. To overcome the risk of breakage, JCVI scientists built the chromosome from a series of 5,000–7,000-bp DNA segments that were assembled into 101 “cassettes.” The chemical synthesis of these segments was outsourced to a pair of companies, Blue Heron Biotechnology of Bothell, Wash., and Geneart AG of Regensburg, Germany. The cassettes, each containing at least one but typically many complete genes, were then linked into progressively larger pieces and eventually combined into an entire *M. genitalium* genome.

Initially, sets of four cassettes were joined to create 25 subassemblies, each of about 24 kb. During that early phase of the project, fragments were cloned as bacterial artificial chromosomes (BACs) in *Escherichia coli*, which produced enough DNA for the next steps as well as for DNA sequence validation.

However, the carrying capacity of *E. coli* proved too small for producing half-genome clones, and the JCVI group turned instead to the yeast *Saccharomyces cerevisiae* to complete this phase of synthesis. Other tests evaluating homologous recombination in *S. cerevisiae* showed it could be used to build bacterial chromosomes from large subassemblies. Indeed, *S. cerevisiae* surpassed expectations at JCVI for its capabilities in assembling and then cloning the one-quarter-genome-sized cassettes into a final synthetic version of the *M. genitalium* genome in a single step. “We don’t as yet know how generally useful yeast will be as a recipient for bacterial genome sequences,” the team members note.

Strategically placed DNA segments serving as “watermarks” enabled the scientists to confirm that the genetic material was synthetic and not native. But the watermarks are also a source of amusement for J. Craig Venter, who assembled the genome-synthesizing team, because they contain encrypted messages that can be deciphered by determining their amino acid sequences. “It’s a fun thing that has a practical application,” he says. Additionally, a 2,514-bp insertion, containing an aminoglycoside resistance gene, was embedded in gene MG408 (*msrA*), both to block pathogenicity and allow for selection.

The genome synthesis project is “a great technical feat and demarcation point for important changes in both genetics and biological engineering,” says Drew Endy, a bioengineer at Massachusetts Institute of Technology in Cambridge, Mass. Citing the “Carlson Curves,” which show that DNA sequencing technology is improving exponentially, with a doubling time of 12–18 months, Endy says he “wouldn’t be surprised if the genomes of bacteria and single-celled eukaryotes were being routinely designed and constructed by 2012.”

However, although Rob Carlson admires the technical achievement, the Seattle, Wash.-based physicist turned molecular scientist who formulated the Carlson Curves notes that technical glitches continue to block efforts by the JCVI team to use their synthetic microbial genome to “boot up” a viable bacterium. The team members first attributed the problem to a vector that interrupted a small gene. After that vector was removed, however, they encountered other technical barriers blocking the full func-
tion of their transplanted synthetic chromosomes.

The next, more difficult challenge facing JCVI scientists is to build a living bacterium with an entirely synthetic genome. Venter predicts this goal will be reached sometime within the year. JCVI researchers already showed that genome transplantation is technically feasible by converting one species of *Mycoplasma* into another (*Microbe*, October 2007, p. 474).

Meanwhile, metabolically engineered designer cells are being used to produce small amounts of a “green,” or environmentally friendly, jet fuel at Synthetic Genomics Inc., in La Jolla, Calif., according to Venter, who serves as its CEO. He expects hundreds of other cell-made products to follow, many of them produced by microbes with laboratory-designed gene cassettes. However, his co-chief scientific officer at JCVI, Hamilton O. Smith, considers it unlikely that *M. genitalium* will ever be employed as a designer organism for such commercial endeavors. “It’s so difficult to grow in the lab,” he points out.

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Microbial Forensics Experts Strive To Develop Validation Procedures

Despite proving useful for identifying anthrax strains used for deadly criminal and terrorist purposes in 2001, the field of microbial forensics requires validation before the courts accept it, according to researchers and other experts who spoke at a meeting, “Microbial Forensics: Nexus between Science, Public Health and Law Enforcement,” held last January in Washington, D.C. The meeting was sponsored jointly by the American Association for the Advancement of Science and the National Academies Committee on Science, Technology and Law.

Microbial forensics holds great promise for providing clues that may help identify culprits behind future bioterror attacks, says meeting participant Randall Murch, a former Federal Bureau of Investigation (FBI) agent who is now at Virginia Tech University’s National Capital Region campus in Alexandria, Va. Conventional forensic analysis proved instrumental in generating leads in terrorist cases, such as the bombing of a federal building in Oklahoma City in 1995, he says. “The same could be true for using microbial forensics on the evidence from a bioterror event.”

However, microbial forensics so far has not been subjected to a court challenge. To withstand the rigorous requirements for evidence in courts, the field will need to undergo validation to show that its analytic techniques deliver accurate, reliable results, Murch and other experts stressed. The key is “validation, validation, validation,” says Judge George Clark, of the Superior Court for the County of San Diego, California, an expert on the use of forensic DNA evidence in legal cases. “That lends great weight in court.”

Several types of validation issues need to be addressed, according to Bruce Budowle of the FBI forensic analysis branch. They include equipment calibration, reproducibility and reliability of techniques, and shipping and storage procedures to ensure microbe samples are not damaged or altered.

In general, microbial forensics requires stricter procedures than those routinely used in academic research, he says.

For example, Paul Keim at Northern Arizona University in Flagstaff and his collaborators, who were doing anthrax research, changed several procedures after they began to work on specimens linked to the anthrax mailings in 2001—instituting lab personnel sign-in sheets and log sheets to track custody of samples. Because so many microorganisms reproduce asexually, their DNA remains mostly unchanged from generation to generation, presenting a challenge to come up with ways, such as mutations, of distinguishing one specimen from another of the same species. In trying to meet this challenge, Keim’s team de-

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### High-Throughput Sequencing Speeds Efforts to Identify Deadly Arenavirus

A previously unrecognized arenavirus, one that is related to lymphocytic choriomeningitis viruses, appears to be responsible for the deaths of three individuals who received transplanted organs from a single donor, according to Ian Lipkin and Gustavo Palacios of Mailman School of Public Health at Columbia University in New York, N.Y., and their collaborators. To track down this lethal but obscure microbial culprit, the researchers relied heavily on “unbiased high-throughput sequencing” of nucleic acids recovered from tissues of two of the transplant recipients. Calling this approach “powerful . . . for the discovery of pathogens,” they say it should not only improve screening of tissues and organs for transplant procedures, but also be useful for identifying “the roots of common chronic illnesses and [to] find deadly bugs.” Details appear in the February 6, 2008 issue of the *New England Journal of Medicine.*
developed an assay for the Ames strain of *Bacillus anthracis* that distinguishes between specimens differing by only one nucleotide. “So we can’t get better, but we need ways to make this more routine,” he says.

The National Bioforensic Analysis Center (NBFAC), which was established within the Department of Homeland Security in 2004, is at the forefront of efforts to standardize microbial forensics. NBFAC facilities under construction at Fort Detrick, Md., will include BSL-2, -3 and -4 labs as well as a BSL-4 repository for samples.

NBFAC director Jim Burans says his lab is “setting a new national standard” for working with microbes in forensic investigations. These efforts include setting special precautions to prevent cross-contamination of microbes and reagents and insisting that personnel use disposable sleeves, gloves, and gowns for each separate lab procedure. Another set of efforts involves accrediting lab groups to conduct particular analytic procedures and techniques.

**Steve Mitchell**
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**Yellowstone Microbes Yield Insights into both Local and Distant Processes**

Microorganisms living in hot springs and geysers at Yellowstone National Park (YNP) are providing insights about biodiversity, microbial ecology, and geomicrobiology, while also furnishing researchers with valuable information about how microbes fit into and, in some cases, help to shape the geochemistry within particular landscapes. Such matters were the focus of scientists who met earlier this year at a hotel inside the park. Their meeting was convened by officials of the National Science Foundation (NSF) and members of the Thermal Biology Institute at Montana State University (MSU), Bozeman.

NSF began establishing Research Coordination Networks (RCN) several years ago as a means for coordinating efforts to characterize, understand, and inventory diverse biota in various settings, including those found within Yellowstone’s 10,000 geothermal sites. A specialized RCN database (www.rcn.montana.edu) helps “scientists to share data about geochemical and microbiological attributes of thermal systems,” says Bill Inskoop, who directs the RCN at MSU, where he is a professor of environmental sciences.

This RCN links data on geochemistry and biology, according to Cristina Takacs-Vesbach, a microbial ecologist at the University of New Mexico, Albuquerque, who led the largest microbial inventory ever conducted at YNP. She and her collaborators surveyed 104 thermal springs across the park—some of them at remote sites—characterizing thermophiles within them and some of their prominent geochemical features, including pH, temperature, and water chemistry.

Their analysis of bacterial 16S rRNA gene sequences uncovered 780 operational taxonomic units, including 576 that occur only at one particular site. The bacterial sequences cover 17 distinct phyla and many unique sequences that do not appear in other databases. “This type of baseline inventory of Yellowstone’s thermophiles is critical for conservation of park resources,” Takacs-Vesbach says. Moreover, “the microbiology lines up with the geochemistry.”

Some microbes favor specific YNP geochemical niches. For example, sulfate reducers are limited to a corridor on the western side of the park, whereas methanogens concentrate in the southwest corner. In an area where a volcano created a caldera two million years ago, microbial and geologic evidence suggests that current thermophilic biodiversity reflects that ancient explosion. “It’s remarkable that geologic events that occurred 2 million years ago are still imprinted on genetic diversity,” Takacs-Vesbach says.

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**First Bollworm Resistance to Bt Made by Genetically Engineered Cotton**

Bollworms, *Helicoverpa zea*, are beginning to develop resistance to insecticidal proteins (Bt), derived from *Bacillus thuringiensis* and being made in genetically engineered (GE) cotton plants, according to Bruce Tabashnik of the University of Arizona, Tucson, and his collaborators. ”This is the first documented case of field-evolved resistance to a Bt crop,” he says, referring to finding dominant resistance among populations of bollworm detected between 2003 and 2006 among more than a dozen crop fields in Mississippi and Arkansas. Bt cotton and Bt corn have been grown on more than 162 million hectares (400 million acres) worldwide since 1996, “generating one of the largest selections for insect resistance ever known,” note Tabashnik and his collaborators. Despite this massive selective pressure, “resistance occurred in [only] one particular pest in one part of the U.S., [and] other major pests attacking Bt crops have not evolved resistance,” he adds. Moreover, newer varieties of GE cotton produce two instead of only one type of Bt, thus overcoming the resistance that has developed. Details appear in the February 2008 issue of *Nature Biotechnology*. 
Microbes at contaminated sites can at least partly detoxify heavy metals such as mercury. What happens at geothermal sites? At some sites within YNP, microorganisms express a mercuric reductase (MerA) gene, releasing mercury that becomes airborne and thus could affect both local and more distant ecosystems, according to Tamar Barkay, a microbiologist from Rutgers University, New Brunswick, N.J. She and her collaborators prospect for MerA sequences in microbial mat samples from seven hot springs in the Norris Geyser Basin area of the park. “What we learn in Yellowstone could apply to other natural environments,” she says.

Some microbial thermophiles, including those found along travertine terraces at Mammoth Hot Springs in YNP, catalyze mineralization, according to Bruce Fouke, a marine geologist at the University of Illinois, Urbana-Champaign. He and his collaborators now use microbe-containing samples from the hot springs to model mineralization in marine organisms such as coral and clams. In water samples from hot springs, several proteins, including heat shock proteins, are known to promote mineralization in clams. Although the cascading travertine terraces in the park look nothing like branching coral reefs, their microscopic structures are identical, and both are made of calcium carbonate. YNP offers a well-grounded promontory for observing this process, particularly because thermophiles in hot pools grow travertine at a rate of five millimeters per day—a great speed advantage over coral growth, which grows a mere one millimeter per year.

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Two Major Circulating Bacterial Pathogens Appear To Be Clonal

Separately but coincidentally, two major types of widely circulating bacterial pathogens appear to be clonal, according to independent research groups, one in the United States and the other based in France.

In the first case, U.S. community-associated (CA) infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is due mainly to a closely similar members of the USA300 group of CA-MRSA strains, according to Frank R. DeLeo of the National Institute of Allergy and Infectious Diseases Rocky Mountain Laboratories in Hamilton, Mont., and his collaborators, whose report was published in the January 29, 2009 issue of *Proceedings of the National Academy of Sciences*. “The USA300 group of strains appears to have extraordinary transmissibility and fitness,” he says. In the second case, approximately 84% of the worldwide cases of Legionnaires’ disease are caused by the single serogroup, Sg1, of *Legionella pneumophila*, according to Carmen Buchrieser of the Institut Pasteur in Paris, France, and collaborators, whose study is published in the February 6, 2008 issue of *Genome Research*. Sg1 isolates contain a common cluster of lipopolysaccharide (LPS) biosynthesis genes even in different genetic backgrounds, suggesting that the gene cluster could be transferred horizontally between strains and possibly allowing them to evade host immune responses, the French researchers point out.

How a Marine Archaea-Bacteria Duo May Cut Methane Emissions

A distinctive whiff of sulfides provided an unexpected dividend for then-graduate student James Moran while he was working with a carbon monoxide-metabolizing archaean methanogen *Methanosarcina acetivorans*. Now at McMaster University in Hamilton, Ontario, Canada, Moran was a graduate student with Christopher House of Pennsylvania State University at University Park. “Our study presents a novel hypothesis that methyl mercaptan is the product of anaerobic methane oxidation and that this compound is then consumed by sulfate-reducing bacteria,” House says. Additional details describing how such methanogens act symbiotically with sulfate-reducing bacteria to oxidize methane coming from deep-sea seeps appear in the January 2008 issue of *Environmental Microbiology* (10: 162–173).

In the late 1970s, researchers first identified consortia of archaeal methanotrophs and bacterial sulfate reducers that oxidize methane. Overall, the sulfate-reducing bacteria help to fuel the archaean oxidation and also release carbon dioxide. Thus, these bacteria reduce sulfate but oxidize methyl sulfide. “These symbiotic consortia live in ocean sediments near methane seeps,” Moran says. “While the archaean use the methane to derive their energy requirements, the by-product of their metabolism is methyl sulfide.
The sulfate-reducing bacteria then consume the methyl sulfide and reduce it to sulfide. . . The potential energy benefits from anaerobic oxidation of methane (AOM) are so small that it is incredible the process can support two metabolisms. Our work offers one hypothesis, that methyl sulfides are shared between the two organisms.

“It appears that AOM is responsible for oxidizing large amounts of methane released from methane hydrates,” Moran continues. Methane hydrates are found frozen in great abundance along the sea floor—up to 22,000 gigatons globally, according to some estimates. When released into the atmosphere, methane is over 20-fold more effective than carbon dioxide as a greenhouse gas. However, although large amounts of methane are constantly being released from ocean-bottom hydrates, AOM keeps its release into the atmosphere relatively low, according to Moran.

An alternative hypothesis is that a ‘reverse methanogenesis’ involving low levels of hydrogen accounts for AOM. When Moran, House, and their collaborators subjected active AOM sediments to elevated levels of hydrogen gas, experiments with isotopically labeled methane indicated that the gas does not play an interspecies role. “Very high pressures of hydrogen do not stop microorganisms from performing the anaerobic oxidation of methane,” House says. “Small amounts of methyl mercaptan do reduce methane oxidation.”

“Without AOM, we could expect much more greenhouse forcing from increased atmospheric methane concentrations,” Moran says. “Understanding this process can help us understand a large portion of the natural system governing global climate, and may help us understand how future changes could affect part of the natural cycles.” However, he points out, “there is currently no documented link connecting AOM to draw down atmospheric methane. While AOM may prevent large amounts of methane from reaching the atmosphere, I am not sure it can actually be responsible for responding to change and bringing down atmospheric methane concentrations.”

The research by Moran and House offers “the first experimental data supporting the case for methyl sulfide serving as an intermediate in the AOM process,” says Ronald Oremland, a Senior Scientist with the U.S. Geological Survey in Menlo Park, Calif. “However, although the data is consistent with what we would expect if this was indeed the case, there are also potential pitfalls with regard to relying too much on this single experimental result.”

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Energy Department Seeks New Means for Deciphering Microbial Genomes

“Knowing the [genomic] sequence is not. . . knowing the biology,” says Edward Rubin, director of the Joint Genome Institute (JGI) in Walnut Creek, Calif. That comment is both jarring and welcome from Rubin, who directs this Department of Energy (DOE) facility that is dedicated to genomic sequencing. It seems reassuring to hear someone in authority say that JGI, now in its second decade of cranking out ever-expanding volumes of DNA sequencing data, works from a more-comprehensive research agenda. With DNA sequencing an important springboard, DOE through JGI and other specialized facilities and programs is seeking innovative means for tapping alternative biological sources for energy—many of them involving microbial players and ingredients, along with those from assorted plants and fungi.

Amid these efforts to harness energy in novel ways, DOE and DOE-supported investigators are also uncovering basic insights into microbiology, according to Rubin and others who spoke during the 2008 Joint Meeting, Genomics: GTL Awardee Workshop VI and Metabolic Engineering Working Group Interagency Conference on Metabolic Engineering, held in Bethesda, Md., last February.

A few days earlier, the Bush administration issued its budget request for the GTL program of $162.7 million for fiscal year (FY) 2009, designating about one-fourth of it for “foundational” research, another one-fourth for developing microbiological or other means for making hydrogen and ethanol more efficiently, and much of the remainder to support programs at several GTL Bioenergy Research Centers.

Projects at JGI currently involve more than 700 research collaborators from other U.S. institutions—mainly from universities but also from national labs and from industry. While microbial genome analysis remains a major component of JGI activities, there are now more than 44 projects that focus on metagenomics, while still others are focusing on plant ge-
nomes, including poplars from distinctive environments as well as sorghum, millet, foxtail, and eucalyptus.

Nonetheless, researchers continue to accumulate microbial DNA sequence data at a rate of about 650 genomes per year, according to Rubin. For many of these bacterial species, especially those from exotic environments, “we have no clue about what maybe half their genes do,” he says. “We’ve got the ‘book,’ but we can’t ‘read’ it. We need new ways to functionally decode gene sequences.”

One such approach entails looking more closely at those microbial genes from disparate species that fail to work when they are cloned matter-of-factly into workhorse strains of *Escherichia coli* as part of routine genomic-sequencing finishing procedures. For several years at least, researchers shrugged off such missing genes as those that were “toxic” to, and thus could not be cloned into, *E. coli*. Typically, they then ingeniously figured out alternative approaches to filling in those sequencing gaps for any particular microbial DNA sequence dataset or another.

Rubin and his collaborators recently turned that seeming technical disadvantage upside down. “In a sense, we’re developing rules for why some genes can’t transfer horizontally into *E. coli,*” he says. “We did a massive search for toxic genes in microbial genomes within the JGI database.” From that analysis, they identified a set of about 2,000 genes, some of which encode small toxic RNA molecules while others encode restriction enzymes (DNA hydrolases) or other kinds of proteins with various antibacterial activities. Rubin and other collaborators, including James Tiedje at Michigan State University in East Lansing, Mich., are continuing to characterize these genes and their biologically active products.

Beyond genome analysis, DOE is supporting research to improve the efficiency of plant energy extraction procedures and also microbial fermentations to produce either ethanol or other organic fuels that, themselves, tend to inhibit those very fermentations, according to Jay Keasling, who heads the DOE Joint Bioenergy Institute in Emeryville, Calif. This institute involves scientists and engineers from several University of California campuses, two National Laboratories in California, and other more distant institutions. Two other similar, DOE-supported, regional research institutes were recently established. One, the Great Lakes Bioenergy Research Center, is based at the University of Wisconsin, Madison (*Microbe*, March 2008, p. 110), while the other, the Bioenergy Science Center, is based at Oak Ridge National Laboratory in Oak Ridge, Tenn.

Major interests at the Joint Bioenergy Institute in California include efforts to re-engineer plants to make them more amenable to digestion by microbial enzymes and other efforts to engineer microorganisms to produce fuels such as alkanes that would be less corrosive and easier to transport by pipeline than is ethanol—as well as less toxic to the microbial hosts producing those fuels, Keasling says. Yet other recent research focuses on

**Assorted News about Viral Pathogens**

Recent developments involving viral pathogens include:

- HIV relies on yet another host receptor molecule, called integrin alpha 4 beta 7, to gain access through T cells to gut-associated lymphoid tissue (GALT), according to Anthony Fauci, Elena Martinielli, and their collaborators at the National Institute of Allergy and Infectious Diseases in Bethesda, Md., whose report appears in the February 2008 issue of *Nature Immunology*. HIV uses at least three other host receptors to infect CD4, CCR5, and CXCR4 cells of the immune system.

- Removing one gene encoding a transcription factor, namely VP30, among the eight along the genome of Ebola virus prevents its growth in cells, making it safer to study options for vaccine and specific antiviral compound development, according to Yoshihiro Kawaoka of the University of Wisconsin School of Veterinary Medicine in Madison and his collaborators, whose report appears online in the January 22, 2008 issue of *Proceedings of the National Academy of Sciences*.

- Cofactors, including bovine viral diarrhea virus-like pathogen and other swine viruses, are helping to increase the virulence of porcine circovirus, according to Roman Pogranichniy of Purdue University in West Lafayette, Ind. and his collaborators.
“ionic liquids” for swelling biomass, allowing better access for microbial enzymes that degrade cellulose.

Jeffrey L. Fox
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Metabolically Halting Sugar Adducts Improves Protein Yields from *E. coli*

Specially targeted, metabolic tweaking greatly boosts protein yields from a strain of *Escherichia coli* that already has proved itself as a workhorse for both research and industrial applications, according to Juan C. Aon and his colleagues at GlaxoSmithKline (GSK) in King of Prussia, Pa. That tweaking overrides a biochemical pathway whereby recombinant proteins are improperly glycosylated—that is, “decorated” with sugar molecules—in ways that interfere with their activity and, thus, require removal. Now, by implementing a novel strategy, the GSK researchers induce the bacterial cells not to make those sugar adducts in the first place. This change not only avoids downstream sugar-removal steps but also improves initial yields of the sought-after proteins. Details of their research appear in the February issue of *Applied and Environmental Microbiology* (74:950–958).

Adducts, in which sugar molecules become covalently bound to proteins, can keep those proteins from folding properly, often blocking their activity and also interfering with their ability to form crystals. Such bad behavior on the part of several such adducts proved frustrating to Aon and other investigators at GSK. Not only was it proving a nuisance for their collaborators, whose X-ray crystallographic work was stalled on two particular proteins, but worse, improper glycosylation was playing havoc with evaluation efforts involving a particularly promising proprietary therapeutic protein.

Typically, when proteins are produced via recombinant DNA procedures in *E. coli* or other microbial cells, the glycosylated proteins are harvested before the sugars are removed. These extra steps inevitably lower the overall efficiency and raise the overall cost of production because some product is lost during each step. Aon and his collaborators figured that they would improve efficiency if they better understood why sugar adducts were forming. They already knew that, in many types of *E. coli* cells, the metabolic intermediate 6-phosphoglucolactone (6-PGLac) can react with newly made proteins to form adducts. However, the enzyme phosphogluconolactonase (PGL) ordinarily breaks down 6-PGLac before it can react with proteins to glycosylate them.

Ironically, the particular workhorse strain of *E. coli*, BL21 (DE3), which is so widely used in industry, produces very little PGL, the GSK researchers learned. Thus, despite its other favorable attributes, this strain produces an excess of glycosylated protein adducts.

To determine whether they could overcome this problem that stymies efficient production of recombinant proteins, Aon and his collaborators further engineered the BL21 (DE3) strain to overexpress PGL. Not only does this change curb protein glycosylation, but it also brought several unforeseen advantages. Thus, overexpressing PGL also leads to an overall increased yield per cell, per unit time of 60% for the protein product, and 50% in the biomass produced per unit of consumed glucose—all this due to the increased activity of PGL.

“I would call this a significant advance, one of many advances that improve the production and safety of therapeutic proteins,” says Arnold Demain of Drew University in Madison, N.J., whose background is in industrial microbiology. “The findings fit in well with the scientific literature, but additionally break new ground in the solution of a practical medical problem [in producing] recombinant proteins of therapeutic value.”

David Holzman
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