THE MIT REPORT

A PUBLICATION OF THE MIT INDUSTRIAL LIAISON PROGRAM

Carbohydrates on Demand?

MIT Production Method Could Help Scientists Target Major Diseases

In the past few decades, scientists discovered how to automatically synthesize proteins and nucleic acids, leading to gene sequencing and the mapping of the human genome. But until now, efficient production of the third class of biopolymers, carbohydrates, has remained elusive. As reported in February in *Science*, MIT chemistry professor Peter Seeberger and colleagues recently developed the first technique to automate the production of these complex sugars. The new process could help researchers better understand how carbohydrates function in the body, and ultimately pinpoint treatments to several major diseases.

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To come up with their ground-breaking method, Seeberger and his team systematically examined and reinvented the process of synthesizing an oligosaccharide, a molecule composed of a chain of simple sugars. Seeberger's system, which he devised with MIT graduate students Obadiah J. Plante and Emma R. Palmacci, consists of a reconfigured peptide synthesizer that automatically attaches one sugar after another. Drawn from small bottles, each sugar is joined to a polystyrene bead containing the growing carbohydrate chain. Whatever fails to react with the beads gets washed away by a solvent. The complex sugar that remains is prepared for further elongation by another chemical reaction. The procedure repeats until the chain is complete.

A Revolutionary Invention

By combining a modified peptide synthesizer with novel reagents that purify and bond simple sugars to one another, Seeberger and his team have sped up oligosaccharide production a hundredfold. "Just as Merrifield's development of automated solid-phase peptide synthesis several decades ago revolutionized the field of protein research, so will this invention accelerate new discoveries in the

MAY 2001
Volume XXIX Number 4

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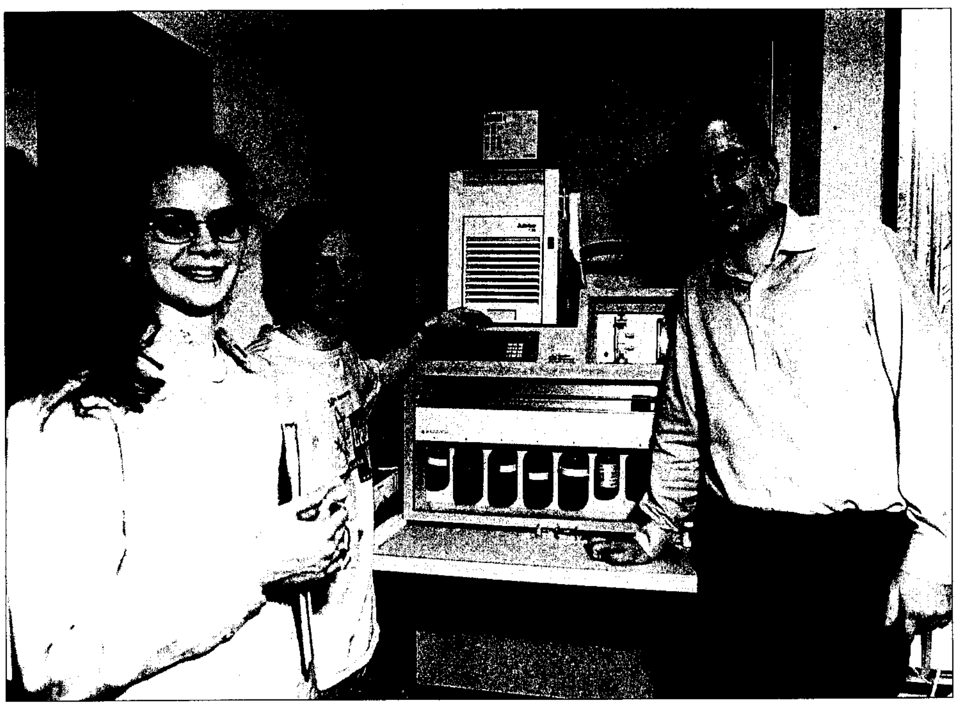
field of glycobiology," says Carolyn Bertozzi, an expert in oligosaccharides at the University of California, Berkeley. "Moreover, the technology may speed the development of oligosaccharide therapeutics, which are gaining significant attention in the biotechnology industry, particularly as vaccine components."

Difficult to access in the body or synthesize in the lab, oligosaccharides loom like a buried treasure for biologists. Past efforts to rapidly produce them have fallen short, either due to problems in purifying the sugars in solution, or in constructing the larger carbohydrate molecules that impact biological processes and diseases. To fashion one by hand entails linking sugar groups that come in a wide variety of three-dimensional shapes, and that bind together in millions of different arrangements. "There are only a handful of chemistry labs that can build these complex and branched biopolymers," observes Bertozzi. "Such high expertise is required that even one skilled in the art of organic synthesis would find oligosaccharides challenging and time-consuming targets."

Indeed, to construct an oligosaccharide that is seven sugars long in a conventional solution could take up to six weeks. But with the new method, "That same carbohydrate took sixteen hours to synthesize, just by pushing a button on a machine," notes Seeberger.



Emma Palmacci, Obadiah Plante, Professor Peter Seeberger, and the synthesizer
Photographed by Donna Coveney, MIT

Targeting Disease

As key agents of communication between cells, carbohydrates play a role in several major diseases, including cancer, HIV, bacterial infections, and tropical illnesses. For example, if you ingest cholera, it gets into your digestive tract. Carbohydrates on the walls of your intestines bind to the cell-surface proteins of the ingested agents, resulting in infection. A better understanding of which carbohydrates are bound by the invader's proteins could lead to drugs that target them before they spread infection.

Carbohydrates may also play a beneficial role. Breastfed infants take in a small amount of sugars, which then coat the cell walls of their digestive tracts. Proteins of invading bacteria bind tightly to these sugars, thus failing to adhere to intestinal cell-surface carbohydrates and infecting the infant. Identifying these sugars and adding them to formula could help prevent several bacteria-borne infectious diseases.

To test how synthesized carbohydrates behave in the cell, scientists will likely track them with a fluorescent label. "We are currently attaching these molecules to surfaces called 'carbohydrate chips,'" says Seeberger. "Then we take a protein or cell and incubate it with that surface to see if it attaches to the surface or not."

Implications for Industry

Recognizing the commercial potential of the new automation process, Obadiah Plante is now forming a company called Advanced Carbohydrate Technologies. "ACT will be an enabling technology platform for several industries," predicts Seeberger, "including pharmaceutical, biomedical, and food processing." For example, the platform could be used to develop drugs targeting infectious and tropical diseases, or to fashion vaccines for cancer; it could help diagnose infectious

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diseases, detect bacteria, or identify agents used in biological warfare; or it could allow food producers to identify the makeup of trace amounts of oligosaccharides when seeking FDA approval of new products. Plante expects that by the end of the year, ACT will be able to fill scientists' call-in orders for specific carbohydrates.

Eventually, Seeberger envisions an advanced version of this platform that could rapidly produce libraries of carbohydrates. Scientists could then systematically test how each carbohydrate in the library impacts cell functioning. But the MIT chemist first aims to assemble a wider repertoire of sugars. "In my lab we want to make this process applicable to all carbohydrates," he says. "We can make a lot of structures right now, but we can't yet make every structure."

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While he refines his technique, Seeberger intends to use it to conduct biochemical and biological studies to better understand diseases and intercellular communication. He is also investigating the synthesis of heparin, a complex sugar that is commonly used to treat heart disease victims, and hopes to extend its use to other diseases, such as cancer and viral infections. Professor Seeberger's work is supported by the Mizutani Foundation for Glycoscience and the Petroleum Research Fund of the American Chemical Society. •

by Mark Dwortzan

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Also, please see the following website: *http://web.mit.edu/chemistry/SeebergerLab/Seeberger_Bioorganic_Chemi.html*

NETSURF

THE MIT CENTER FOR ADVANCED NUCLEAR ENERGY SYSTEMS

http://web.mit.edu/canes/

The MIT Center for Advanced Nuclear Energy Systems (CANES) has updated its website (dated 2/2001). CANES was established by the Department of Nuclear Engineering and the MIT Energy Laboratory to create a better understanding through research of nuclear energy systems that promise more favorable economics, safety, proliferation resistance, and environmental impact. The Center's programs involve development of methods for the design, operation, and regulation of current and advanced nuclear reactors and fuel cycles. This requires advances in knowledge about traditional scientific and technical disciplines, about modern methods of systems reliability and decision analysis, as well as about human interactions and management science.

LABORATORY FOR COMPUTER SCIENCE

http://www.lcs.mit.edu/

The Laboratory for Computer Science (LCS) has recently updated its web pages (now quite similar to MIT's home page), and the link "About LCS" provides a list of spinoff companies which includes the name(s) of founder/co-founder and date of inception. LCS brings together faculty, researchers, and students in a broad program of study, research and experimentation. Its members pursue innovations in information technology that will yield substantive long-term improvements in the ways that people live and work. LCS strives for excellence, relevance, and social purpose. The hallmark of its research is a balanced consideration of technological capability and human utility.

MIT CENTER FOR REAL ESTATE

http://web.mit.edu/afs/athena.mit.edu/org/c/cre/www/

The MIT Center for Real Estate was founded in 1983 within the School of Architecture and Planning. It sponsors a full agenda of research on issues related to real estate development, investment, and management. The Center also serves as the base for the Master of Science in Real Estate Development, an interdepartmental degree program that educates students to assume positions of responsibility, in both public and private sector real estate organizations. The Center's faculty are drawn from the School of Architecture's two departments—Architecture, and Urban Studies and Planning—and from the Department of Economics, the Department of Civil and Environmental Engineering, and the Sloan School of Management.