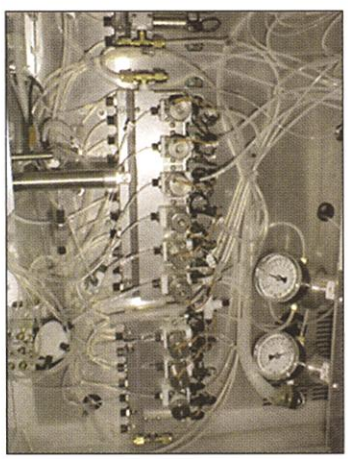
ORGANIC CHEMISTRY

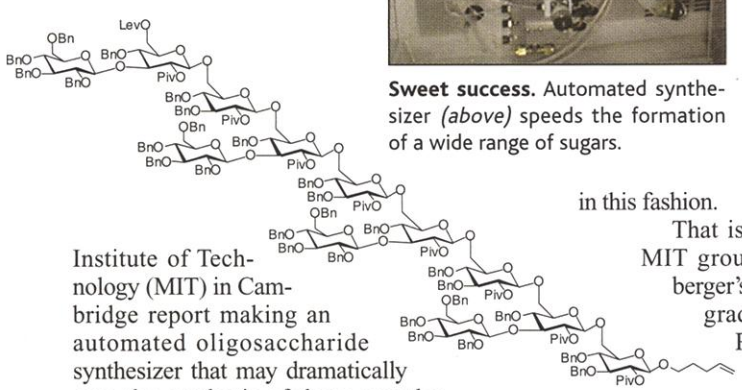
# Sugars Join the Automation Rush

For many biologists, sugars aren't so sweet. Chains of these simple molecules, called oligosaccharides, are vital to communication and binding between cells. But even short oligosaccharides are extremely difficult to synthesize. The inability to cook up large quantities of these molecules to conduct experiments has long kept researchers in the dark about what many of them do in the body. Indeed, when specialists in immunology, cancer biology, and developmental biology encounter oligosaccharides, they often just steer their research in another direction. "A lot of times they just stop working on the problem and do something else," says Carolyn Bertozzi, an oligosaccharide expert at the University of California, Berkeley. But now they are likely to get some help.

In a paper published online by *Science* this week (www.sciencexpress.org), Peter Seeberger and his students at the Massachusetts Institute of Technology (MIT) in Cambridge report making an automated oligosaccharide synthesizer that may dramatically ease the synthesis of these complex chains. Seeberger's team, for example, created one oligosaccharide made of 12 sugar units in 18 hours. Conventional methods would take months. Enabling researchers to mass-produce oligosaccharides and test their effects on cells, Bertozzi says, is likely to revolutionize the understanding of the role of these molecules in immunology, cancer biology, tissue development, and intercellular communication.



**Sweet success.** Automated synthesizer *(above)* speeds the formation of a wide range of sugars.



Similar widespread benefits ensued when researchers automated the synthesis of the two other classes of biopolymers, nucleic acids and peptides. Oligosaccharides, however, have remained automation's holdout—not for lack of interest, but because they link together in myriad complex three-dimensional shapes. Whereas the building blocks of nucleic acids and peptides bind in linear chains like boxcars on a train, the sugars in oligosaccharides have numerous points of attachment, like a child's Lego blocks. A single glucose unit, for example, has four hydroxyl groups that can bind to other sugars. What's more, each bond that forms between separate units can take one of two different shapes. As a result, just four sugars can be strung together in more than 5 million possible arrangements, says Chi-Huey Wong, an oligosaccharide chemist at the Scripps Research Institute in La Jolla, California.

Organic chemists typically deal with this problem by capping sugar molecules with "protecting" groups at all but one reaction site to block unwanted reactions. That precaution ensures that the bond is placed at the right spot when two sugars react. But it still leaves compounds with a mixture of bonds formed in different orientations, requiring laborious purification procedures after each new sugar building block is added. To streamline the process, numerous groups have recently experimented with growing oligosaccharides on solid supports and using protecting groups that force the molecules to bond in just one orientation. It can take just 2 weeks to make a 12-unit chain in this fashion.

That is the procedure that the MIT group has automated. Seeberger's team—which included graduate students Obadiah Plante and Emma Palmacci—converted an old peptide synthesizer to work with the new sugar-based reagents and reaction conditions. Along the way, the team invented new protecting groups that work better with solid supports, a novel linker group that holds on tight to the oligos but can easily be clipped at the end of the process, and novel reactants that knit sugar bonds together.

The team starts by hooking the linker to a polystyrene bead. The synthesizer then introduces an initial sugar building block that reacts with the linker. After a washing step removes unwanted byproducts, additional reagents remove a targeted protecting group on the sugar, opening a site for the next sugar unit to bind. The process is repeated until the desired oligo is made.

Thus far the MIT team has used the approach to make oligosaccharides with four of

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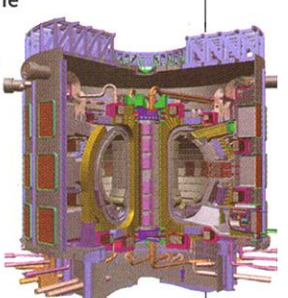
## ScienceScope

**Aussie Windfall** Researchers are applauding a $1.6 billion plan for Australian science. The 5-year government roadmap, released this week, largely follows recommendations from two reports issued last year by researchers and industry to reverse cuts and strengthen education, research, and the commercialization of new technologies (*Science*, 13 October 2000, p. 255).

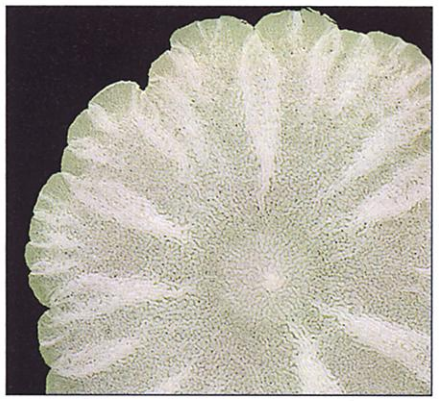
The plan calls for doubling basic research spending by the Australian Research Council to $300 million in 2006 and nearly doubling funding for university infrastructure to $108 million. It also includes funds to support 21,000 new undergraduate students in math, science, and information technology, and for new IT and biotechnology research centers. Responding to complaints about earlier cuts, the government also plans to bump up tax credits and subsidies for industrial R&D.

Government chief scientist Robin Batterham, who wrote last year's scientists' report, is "delighted" by the plan. "Virtually all the recommendations of [our] report have come through," he says.

**Fusing Behind Fusion** European Union research ministers have united behind plans to build an International Thermonuclear Experimental Reactor (ITER). Last year, after the United States backed out of the megaproject, E.U. ministers couldn't agree on whether to move ahead with the $3.7 billion tokamak, a device designed to test the feasibility of fusion power. But at a special meeting in Brussels last month, officials agreed to put funding for the project—which is also backed by Japan and Russia—into the E.U.'s next 5-year Framework research plan, which begins in 2003.



Exactly how much Europe will spend on ITER, however, will depend on where it is built. Japan, France, and Canada are interested in hosting the machine, which means shouldering a greater share of the cost. E.U. officials say their existing $500 million fusion budget could handle an expected contribution to a machine built outside Europe, but not to a regional facility. ITER's partners hope to settle on a site by the end of 2002 and complete the device by 2014.



**Flowering research.** Bakers' yeast biofilms may serve as models of those formed by dangerous fungi.

grows steadily outward from a central disc. After a few days, lightly colored spokes appear, consisting of cells that for unknown reasons grow somewhat slower than other cells. This results in a scalloped outline that leaves the mat looking like a flower.

The researchers identified one type of protein the cells need to stick to a surface and to each other. They found they could prevent the yeast from forming sturdy biofilms by mutating either of two genes, *FLO11* or *FLO8*, needed to build a glycoprotein that is located on the cell surface and is known to allow yeast cells to adhere to agar.

Reynolds says he and his colleagues now hope to figure out which genes impel the fungi to band together in the first place and then progress through various stages of biofilm construction. If comparable genes can be found in pathogenic fungi, they would be good targets for preventing biofilm formation. Kolter thinks the approach makes a lot of sense, particularly because different species of fungi tend to use the same sets of tools. Ideally, finding a way to keep dangerous fungi divided will allow them to be conquered. **–LAURA HELMUTH**

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RICE GENOME

## Syngenta Finishes, Consortium Goes On

A Swiss-based agrochemical company has completed sequencing the genome of the first important food crop, rice. But scientists who want the data will either have to pay for the right to use it or wait 3 years until an international consortium completes its work on a publicly sponsored—and likely more thorough—version of the same project.

Last week, Syngenta AG of Basel, Switzerland, announced that it had sequenced the majority of the 430 million bases of the rice genome. The work was overseen by its scientists in California and carried out mainly by Myriad Genetics Inc. of Salt Lake City, Utah. The project took 14 months, 6 months faster than planned, and came in under budget, although the company won't divulge the total cost. The results outpace the efforts of the International Rice Genome Sequencing Project, led by Japan, which hopes to finish its work in 2004 at an estimated cost of $100 million.

"On a technical level, they should be very proud," says Rob Martienssen of Cold Spring Harbor Laboratory in New York, a member of the international consortium. "Their coverage is very good, and it's certainly a lot of sequence, but it's still very far from a complete sequence." The Syngenta project sequenced each nucleotide an average of six times. To assure a complete, continuous sequence without gaps, however, each nucleotide needs to be sequenced 10 or 12 times.

In December, plant geneticists announced the complete genome sequence of the first higher plant, *Arabidopsis thaliana*, the model organism of choice for basic plant research but with no commercial value. In contrast, says Steven Briggs, head of the Torrey Mesa Research Institute in California—the genomics research arm of Syngenta—knowing the rice genome should allow scientists not only to improve rice varieties but also to find similar genes expressed in related cash crops such as wheat and barley.

The Syngenta rice map "will not be in the public domain," says Briggs. Instead, Syngenta will provide academic researchers access through scientific collaborations, in return for a share of any commercial inventions stemming from the research. Syngenta also says that it will provide information and technology to the developing world for improving subsistence farming. But Martienssen says the value of Syngenta's work is diminished by its relative inaccessibility: "If it's not really a general public resource, and if it can't be searched, it doesn't have the same impact."

Syngenta has worked with the public rice consortium before, funding work to sequence the ends of the bacterial artificial chromosomes used as the primary template for sequencing. And it's not the only commercial player. Last April, Monsanto finished its own rough draft of the rice genome, which has 4× coverage, and made its data available to the international project.

Getting access to the Monsanto data has allowed the international project to advance its estimated completion date by 4 years. And Japanese members leading the effort on chromosome 1 (of 12) plan to announce their results in March. Takuji Sasaki, director of Japan's rice genome research program, hopes to find ways to accelerate the sequencing but says "it will take additional funding." Adds Martienssen, "We shouldn't sacrifice accuracy or completeness just to speed up."

**–R. JOHN DAVENPORT**

## ScienceScope

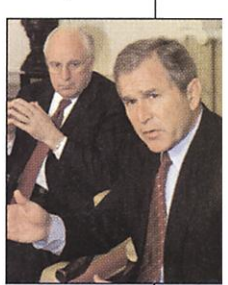
**Whistleblower Blowup** A government proposal to protect people who report scientific fraud from retaliation is drawing harsh criticism. The Federation of American Societies for Experimental Biology (FASEB) and another group claim that the whistleblower rule proposed by the Department of Health and Human Services (HHS) would be a nightmare to implement.

The draft rule, required by a 1993 law, lays out a detailed process that institutions must use to resolve whistleblower complaints within 30 to 60 days. But the rules are "overly prescriptive," FASEB president Mary J. C. Hendrix wrote in a letter to HHS on 29 January. Hendrix noted that the rule may conflict with other laws, favor accusers over the accused, and prove expensive. The Council on Governmental Relations, which represents 143 research universities, sent a similar letter. "I've never had so many calls from [university] general counsels," says executive director Kate Phillips.

Chris Pascal, head of HHS's Office of Research Integrity, declined comment. A final rule could come later this year, pending review by the new Administration.

**Unclear Forecast** President George W. Bush kept scientists guessing last week about the fate of federal funding for stem cell research. In his first comment on the issue since taking office, Bush said on 26 January that "there are some wonderful opportunities for adult stem cell research," and that "I believe we can find stem cells from fetuses that died a natural death. And I do not support research from aborted fetuses."

He did not say whether he would block a National Institutes of Health (NIH) plan to fund research on the cells, which could help treat many diseases. And he was silent on cells derived from another controversial source: "excess" embryos slated for disposal at fertility clinics. Aides, however, said Bush was signaling his intent to block NIH's plan.



But stem cell enthusiasts still had reason to hope. Bush's choice for secretary of Health and Human Services, Tommy Thompson, who will oversee NIH, has in the past supported embryonic stem cell research. And in Congress, Senator Arlen Specter (R–PA), a vocal supporter of stem cell research, intends to reintroduce a bill that would allow NIH's plan to go forward. Last year, opponents blocked debate on a similar measure.

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