launch vehicle. The project has won the support of Indian Prime Minister Atal Behari Vajpayee, who in December touted his government's intention to build "a multiwavelength observatory to conduct front-ranking research in astronomy." –PALLAVA BAGLA

MICROBIOLOGY

## Possible New Route to Polyketide Synthesis

For researchers prospecting for new drugs, one class of natural compounds—the polyketides—has long been the mother lode. These drugs, including such therapeutic mainstays as the antibiotic erythromycin, the immunosuppressive drug FK506, and the cholesterol-lowering drug lovastatin, have combined sales exceeding $10 billion per year. Now, researchers may have hit another rich vein: an improved method of synthesizing and engineering polyketides.

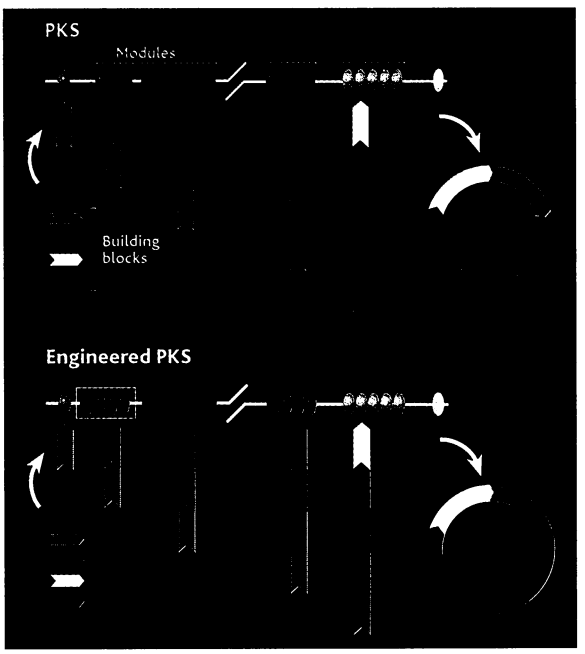
The compounds are difficult to synthesize, forcing drug companies to rely on production by their natural sources—unusual soil bacteria and fungi. Some of these microbes can be cultured readily, but many others are slow-growing and finicky, which makes them difficult to grow in the huge vats needed for industrial production. They're also tricky to alter genetically, hampering efforts to tweak the polyketide-synthesizing enzymes so that they make new variants. But on page 1790 of this issue, chemical engineer Chaitan Khosla of Stanford University and his colleagues report that they've engineered the common lab bacterium *Escherichia coli* to pump out a polyketide at rates potentially useful for industrial drug production.

Because *E. coli* is both easy to grow and highly amenable to genetic manipulation, the results offer a possible way of producing polyketides from exotic microbes in a much more tractable host. They also offer an opportunity to engineer new versions. "I think it's a real breakthrough," says bioorganic chemist Heinz Floss of the University of Washington, Seattle.

To pull it off, Khosla and his colleagues, Stanford graduate student Blaine Pfeifer, David Cane of Brown University in Providence, Rhode Island, and two others, had to overcome a series of formidable hurdles—adding the machinery for two new metabolic pathways and crippling another in *E. coli*.

The first problem was getting *E. coli* to make the enzyme that synthesizes the researcher's target polyketide, which forms the core of erythromycin. In nature, the bacteria that produce polyketides, in this case, a soil bacterium called *Saccharopolyspora erythraea*, rely on an unusual enzyme. This enzyme, polyketide synthase, sequentially joins a series of small building blocks to form the eventual product, which is a circular molecule. The enzyme itself consists of three very large proteins. As a result, the researchers had to introduce three *S. erythraea* genes into *E. coli* and fine-tune growth conditions just to make the enzyme.

The next challenge was getting the polyketide synthase to work in *E. coli*. These enzymes behave much like an assembly line, passing a growing polyketide chain from one active site to the next to add the next building block. The enzyme uses a cofactor compound called phosphopantetheine to carry out this transfer. But on its own, *E. coli* couldn't add the phosphopantetheine to polyketide synthase. To coax it to do so, the researchers added a gene from the soil bacterium *Bacillus subtilis* that produces another enzyme that attaches the cofactor.




**Mix and match.** By swapping or changing the modules that contain the active sites of polyketide synthases, researchers could engineer the enzymes to make novel polyketides in *E. coli*.

SOURCE: KOSAN BIOSCIENCES INC.

Finally, two modifications were needed to provide *E. coli* with the building blocks it needed to make the polyketide. To supply one, called propionyl coenzyme A (propionyl-CoA), the Stanford team knocked out key *E. coli* genes to cripple a metabolic pathway that breaks down that compound. To supply the other, called methylmalonyl-CoA, the Stanford team borrowed a gene from a third soil bacterium. If any one of their tricks had failed, the researchers would have had to start over. "We kept our fingers crossed to the very end," Khosla says.

Their efforts paid off, resulting in a bacterial strain that can pump out the polyketide at rates approaching those of industrial *S. erythraea* strains. In addition, by replacing one component of the *S. erythraea* polyketide synthase with a portion of an enzyme that makes a different type of drug, the Stanford team generated a hybrid enzyme that makes a polyketide unlike any found in nature. "They've demonstrated the feasibility of a directed approach" to making new polyketides, says microbiologist Joan Bennett of Tulane University in New Orleans, Louisiana, president-elect of the Society for Industrial Microbiology.

If *E. coli* can be used as a factory for making either natural or designer polyketides, the work could lead to a big payoff for Khosla and a company he co-founded, Kosan Biosciences of Hayward, California. Kosan owns the patent for the method and has the option of commercializing the discovery under a license agreement with Stanford. "We're going to ask now if we can use *E. coli* on a very large scale," says microbiologist Richard Hutchinson, Kosan's vice president of new technology.

Khosla and his colleagues still have a way to go to get industrial polyketide production by *E. coli*. They need to coax the microbe to add sugars to the polyketide to generate a complete erythromycin molecule. And if they accomplish that, Floss cautions, there's a chance that the antibiotic will kill the bacteria producing it. Khosla maintains that there are ways around those problems, such as having chemists add the sugars or stitching erythromycin-resistance genes into *E. coli*. "The important thing for people to realize is that it's not difficult anymore" for researchers to devise and produce new polyketides, Khosla says. If so, then the work may trigger another gold rush of polyketide prospectors.

–DAN FERBER

CELL BIOLOGY

## Nobel Laureates Lobby for Stem Cells

Eighty Nobel Prize winners have signed a letter urging President Bush to allow government-funded researchers to work on human pluripotent stem cells. In a letter faxed to the White House on 22 February, they argue that the cells—which have the capacity to develop into any tissue type—could help treat a variety of diseases. The Bush Administration is under pressure from antiabortion groups to block federal funding for work on embryonic stem cells.

Scientific teams around the world are

working on strategies to prompt stem cells to become specific cell types—neurons, muscle, or pancreatic cells—that could treat diseases such as Parkinson's or diabetes. The most controversial research has been conducted on cells derived from aborted fetuses or days-old human embryos; in other cases, stem cells from adults have been used. Opponents of embryonic or fetal tissue research argue that adult stem cells could offer the same benefits without the ethical problems, but the Nobel laureates' letter calls this assertion "premature." Stem cells from adults may prove very useful, says signatory Paul Berg, a biochemist at Stanford University, but "we can't ignore the potential of embryonic stem cells. ... We should be proceeding full-speed along both tracks."

Bush has ordered the U.S. Department of Health and Human Services to review existing National Institutes of Health (NIH) policy. Under this policy, which was developed last year, government-funded researchers may not derive human embryonic stem cells but can use them if they are obtained from privately funded scientists who prepared the cells in accordance with a set of ethical guidelines (*Science*, 1 September 2000, p. 1442). (For example, applicants must certify that the cells were derived from embryos that were created for fertility treatments but were slated to be discarded.) The next deadline for submitting applications for embryonic stem cell research is 15 March, and, barring a change in policy, applications will be reviewed by an ethics board in April.

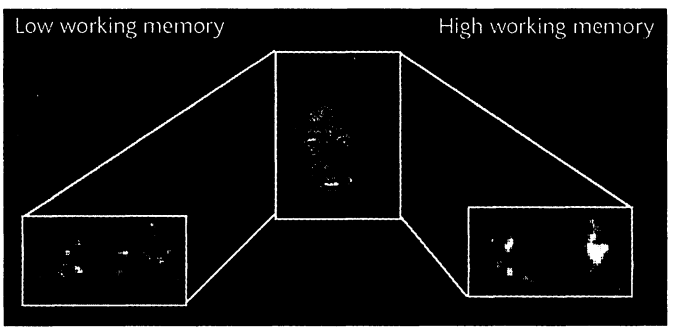
The letter was written and circulated by researchers Robert Lanza and Michael West of Advanced Cell Technology, a biotech company in Worcester, Massachusetts, that works on cloning and stem cell research. The duo, with many of the same laureates, signed a similar letter in 1999 urging the U.S. Congress and the Clinton Administration to support plans at NIH to fund work on stem cells (*Science*, 19 March 1999, p. 1849). That letter was "successful," says Lanza, who hopes the current one will show the president that "the scientific community is unified in support of this research." –GRETCHEN VOGEL

NEUROBIOLOGY

# Working Memory Helps the Mind Focus

When traversing city streets, a driver needs to focus on important information—say, a red light or a car veering into the lane—rather than irrelevant images such as the type of tree lining the road. New work now provides a better understanding of just how the brain achieves such feats of selective attention—information that may have both public health and medical implications.

In experiments described on page 1803, cognitive psychologist Nilli Lavie of University College London and her colleagues have pinpointed a surprising new influence on a person's ability to focus: working memory, which is where the brain temporarily stores information used in reasoning and planning. In both behavioral and brain-imaging studies, the researchers have demonstrated that when a person's working memory is occupied, his or her brain cannot filter out distracting sights in a separate attention task.




**Distracted.** The greater stimulation of the visual areas at the back of the brain shows that the brain is more distracted by an image, such as that of former U.S. President William Clinton, when working memory is full (right image) than when it is less occupied.

Researchers had suspected that parts of the brain involved in conscious planning, such as working memory, might play a role in selective attention, but they did not know how. For the first time, Lavie's work provides "direct evidence that the working memory system is modulating attention and affecting processing within the brain's object recognition system," says neuroscientist Robert Desimone of the U.S. National Institute of Mental Health in Bethesda, Maryland.

The new findings could also have implications for the debate over cellular telephone use in cars. So far, safety measures have largely centered on getting drivers to use telephone headsets or speakerphones. But the new study suggests that the availability of one's hands may be only a small part of the solution. If a phone conversation requires any thought, it will tax working memory and may therefore cause a driver to be more distracted by irrelevant sights on the road.

When Lavie began this research in the late 1990s, she was trying to identify the environmental factors that might influence a person's ability to screen out visual distractions. She had discovered, for instance, that this was easier when the scene was busy than when a person had to focus on fewer objects; this is because people become more focused when the task is harder. But because a person's ability to concentrate seems to vary even when the scene stays constant, Lavie knew that the scene's complexity couldn't be the whole story.

Indirect evidence suggested that working memory might also play a role. In monkeys, for example, neurons in the prefrontal cortex, where working memory resides, seem to fire only in response to visual stimuli relevant to a given task. In addition, anatomical links between the prefrontal cortex and visual regions at the rear of the brain could mediate the hypothesized interaction between working memory and brain areas known to be involved in detecting objects.

To test the idea more directly, Lavie and postdoc Jan de Fockert first devised a task that required selective attention. They flashed the names of pop stars and politicians in front of 10 volunteers, asking them to choose the profession of each person named. As each name was flashed on the screen, the researchers also showed the volunteers a picture of a face that might or might not match the name. This forced them to try to ignore the face and focus on the text. As expected from previous work, the volunteers took significantly longer to answer when the face didn't match the name than when it did, a measure of the influence of the distracting face.

To investigate working memory's involvement, the volunteers also had to memorize a string of five digits, which they were asked to recall right after the attention task. When the number string was easy, such as 0 1 2 3 4, volunteers could remember it without taxing their working memories; as a result, they could classify the pop stars and politicians as quickly as they could in the absence of the memory task. However, when the digits were more random—say, 0 3 4 2 1—the volunteers had to continually rehearse them in their minds, putting a heavy load on their working memories. In this situation, they took much longer to determine whether a name belonged to a pop star or a politician in the presence of a nonmatching face.

To see how this played out in the brain, Lavie and de Fockert teamed up with brain imaging experts Christopher Frith at the nearby Institute of Neurology and Geraint Rees, now at the California Institute of Technology in Pasadena. The researchers used functional magnetic resonance imaging to measure brain activity while six new volunteers performed the tasks.

As expected, the researchers detected more activity in the prefrontal cortex when working memory was heavily taxed than when it was not. They also found that the dis-

CREDIT: DE FOCKERT *ET AL.*