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.

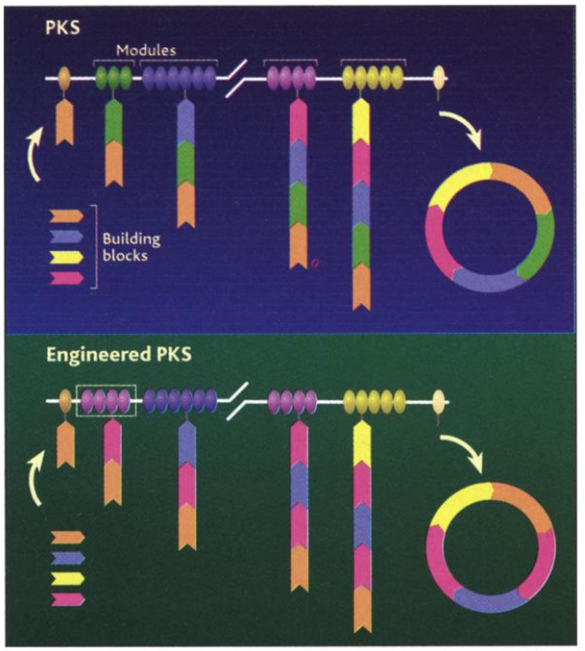
The compounds are difficult to synthesize, forcing drug companies to rely on production by their natural sources—unusual soil bacteria and fungi. Some of these microbes can be cultured readily, but many others are slow-growing and finicky, which makes them difficult to grow in the huge vats needed for 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