NEWS

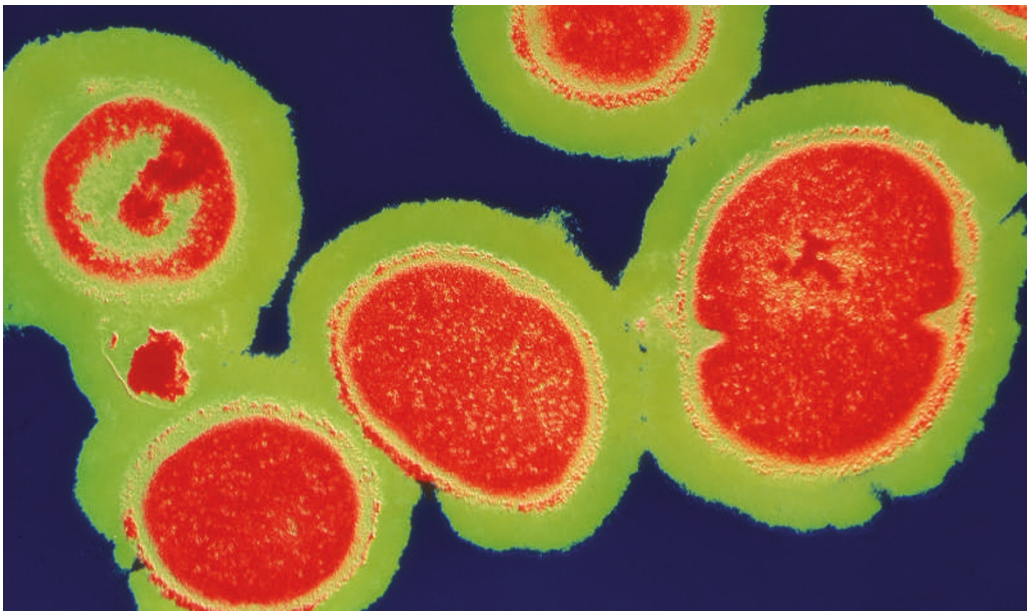
Antibiotic faces uncertain future

A promising new antibiotic is generating both excitement and despondency. It is the first new chemical class of antibiotic to be found in more than two decades, but experts fear that the hurdles to turning the compound into an effective commercial drug could mean that it ends up collecting dust on a shelf.

The drug, called platensimycin and reported on page 358, kills several of the major drug-resistant bacteria that plague hospitals. Among them are methicillin-resistant *Staphyloccocus aureus* (MRSA) and bacteria resistant to vancomycin, one of the last lines of antibiotic defence.

Only two other new chemical classes of antibiotic have been discovered and approved for use since the early 1960s: daptomycin and linezolid. Most antibiotics used today were discovered in the 1940s and 1950s, and newer versions have mainly been made by chemically nipping and tucking these compounds. They generally kill bacteria by blocking the production of proteins, DNA or the bacterial cell wall.

Platensimycin has a novel chemical structure and works differently from other commercially available antibiotics by crippling FabF, a bacterial enzyme involved in manufacturing fatty acids. It thus stops bacteria from making the fatty cell membranes they need to grow. Two commercially available antibiotics, triclosan and isoniazid, target another enzyme involved in fatty-acid synthesis, but these do not kill the same array of bacteria.



An antibiotic has been discovered that kills the deadly methicillin-resistant *Staphylococcus aureus*.

K. LOUNATMAA/SPL

The researchers at Merck Research Laboratories in Rahway, New Jersey, who discovered platensimycin, did so by reviving and tuning an established strategy. They searched for naturally existing compounds that microbes typically make to kill neighbouring bacteria. This

Neanderthal DNA yields to genome foray

NEW YORK

The first nuclear DNA sequences from a Neanderthal (*Homo neanderthalensis*) have been reported. The results should provide clues about when certain diseases, or traits such as hair or skin colour, arose. They also have geneticists excited about the idea of sequencing a Neanderthal genome.

Svante Pääbo, a palaeogeneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, began his Neanderthal Genome Project about two years ago. He and his team have probed 60 Neanderthal specimens from museums for hints that the DNA might have survived millennia of degradation. The species lived across Europe and western Asia from 300,000 to around 30,000 years ago, with the first specimen found in 1856 near Dusseldorf, Germany.

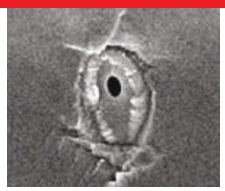
Two of the specimens showed promise, and on 12 May Pääbo's team reported at the Biology of Genomes meeting at New York's Cold Spring Harbor Laboratory that they had managed to sequence around a million base pairs of nuclear DNA — around 0.03% of the genome — from one of them. This is a 45,000-year-old male specimen found in Vindija Cave outside Zagreb, Croatia.

Typically, DNA to be sequenced must be cloned in bacteria to produce large enough amounts for study. But because the Neanderthal DNA had broken down into tiny fragments, Pääbo and his colleagues used a new sequencing technique, developed by 454 Life Sciences in Branford, Connecticut, that allows genetic fragments in an emulsion to be sequenced directly in tiny wells. They are now analysing the results to work out how the different fragments fit together so that they can be compared with the modern human genome sequence.

One finding so far is that the Neanderthal Y chromosome is substantially more different from human and chimp Y chromosomes than are other chromosomes. This suggests that little interbreeding occurred, at least among the more recent Neanderthal species.

Edward Rubin, director of the Joint Genome Institute in Walnut Creek, California, works with Pääbo. The two are also working to sequence Neanderthal DNA by the traditional method. James Noonan, a postdoc in Rubin's lab, reported at the Cold Spring Harbor meeting that preliminary analysis of the 75,000 base pairs sequenced so far shows that Neanderthals diverged from the lineage that led to modern humans about 315,000 years ago — around the time that had been thought. *Homo sapiens* is known to have evolved at least 200,000 years ago (I. McDougall, F. H. Brown and J. G. Fleagle *Nature* 433, 733–736; 2005).

Back in 1997, Pääbo reported sequencing the first mitochondrial DNA from a Neanderthal (M. Krings *et al. Cell* 90, 19–30; 1997). That sequence also suggested that Neanderthals split from the



S. JUODKAZIS *ET AL.*

RECORD-BREAKING LASER IS HOT STUFF
The record for the fastest rise in temperature has just been topped.
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technique originally yielded many potent antibiotics, but was abandoned by many drug companies as the rate of return diminished and has been replaced by chemical methods to generate novel synthetic molecules.

Traditionally, researchers have tested whether a tiny amount of chemical can kill off a circle of bacteria growing on a plate. But by first making the bacteria more vulnerable, the Merck researchers searched for natural products that might have been missed in such conventional assays. They engineered *S. aureus* bacteria to make less of the FabF enzyme than normal, using a snippet of RNA to block the production of this protein (K. Young *et al. Antimicrob. Agents Chemother.* **50,** 519–526; 2006).

The researchers then tested whether any of 250,000 natural-product extracts could block the growth of the disabled strain — and pulled out platensimycin, a small molecule made by a strain of *Streptomyces platensis* bacteria in a South African soil sample. "It allowed us to find a needle in a haystack, and something we might have missed with another type of screen," says Stephen Soisson, one of the lead researchers.

"Platensimycin's discovery highlights the fact that compounds are still waiting to be found."

Other scientists are delighted with the new compound, and say it could provoke renewed interest in natural compounds and in attacking the fatty-acid synthesis pathway. "From a scientific point of view it is what you want — a new class against a new target," says Steven Projan of Wyeth Research in Pearl River, New York.

But "the next steps are fraught with danger", warns microbiologist Carl Nathan of Weill Medical College of Cornell University in New York. "The obstacles are truly formidable."

Platensimycin could stumble at one of many scientific, regulatory or financial hurdles. One concern is that it may be unstable in the body, because the research team had to infuse it continuously into mice to rid them of a *S. aureus* infection. The chemical might need extensive modification to make it more stable, and could prove useless if it has toxic side effects.

Testing antibiotics in clinical trials is also tough and expensive. This is partly because the US Food and Drug Administration (FDA) does not have clear guidelines for approving new antibiotics, says Frank Tally, chief scientific officer of Cubist Pharmaceuticals in Lexington, Massachusetts, which developed daptomycin. Even if platensimycin is approved for human use, it will probably meet the fate of its predecessors, as bacteria rapidly acquire resistance to it. "It might make it to the clinic and then fade because of drug resistance," Nathan says.

With such a daunting task ahead, some microbiologists fear there is little incentive for Merck to develop the drug. Not only is the process hugely expensive, but the potential market for a new antibiotic — which is often used sparingly and administered for only a week or two — is small. This has prompted many pharmaceutical giants to cut back their antibiotic research programmes in recent years.

The Merck researchers refuse to spell out their plans for platensimycin, although they hint that they are working on it. "We are still in the business of doing antibiotic research, and we wouldn't be if we didn't want to develop our own compounds," says Sheo Singh, another of Merck's lead researchers.

Several solutions have been proposed to keep new drugs flowing into the clinic as microorganisms overcome old ones. The Infectious Diseases Society of America proposed an array of regulatory measures in 2004 that might entice drug companies to develop antibiotics, such as revised FDA standards for the approval of antibiotics and tax breaks for work on such drugs (see *Nature* **431,** 892–893; 2004). Some researchers are turning to alternative measures to fight life-threatening bacteria, such as microbe-killing bacteriophage and vaccines.

But many workers still think that novel antibiotics remain the best tried and tested way to combat microbes. They say platensimycin's discovery highlights the fact that compounds are still waiting to be found. "With a paper like this, people might start to reinvest in this area," Tally says, as it shows that new molecules can be found in well-known sources. ■

Helen Pearson

common lineage well before modern humans evolved and may not have contributed any mitochondrial DNA, at least to modern humans.

But the more extensive nuclear DNA sequences should pin down the timing of the split more precisely, and comparing genes for particular traits could help researchers work out which characteristics were shared by Neanderthals, and when such traits arose. Such comparisons could also confirm whether Neanderthals did contribute isolated genes to the human lineage. For example, John Hardy, a geneticist at the National Human Genome Research Institute in Bethesda, Maryland, has hypothesized that Neanderthals may have contributed a gene that is linked to several neurodegenerative diseases, because it is found in people of European ancestry, where the Neanderthals lived. Proving that theory would require finding this version of the gene in the Neanderthal genome.

Researchers are confident about the prospects for sequencing much more Neanderthal DNA. "Our goal is to sequence a large amount of the Neanderthal genome," says Pääbo. That task will probably require identifying new fossils. "We should do it," agreed Francis Collins, director of the National Human Genome Research Institute, after attending Pääbo's lecture on 12 May.

Rubin says he envisages creating a bank of Neanderthal DNA, so that representative samples can be compared with the thousands of *H. sapiens* genomes that are expected to be sequenced in the future. "In ten years, we hope to have ten Neanderthal genomes," says Rubin. ■

Rex Dalton

G. J. SAWYER & B. MALEY; PHOTO D. FINNIN/AMNH

Neanderthal (right) DNA should shed light on the human genome.