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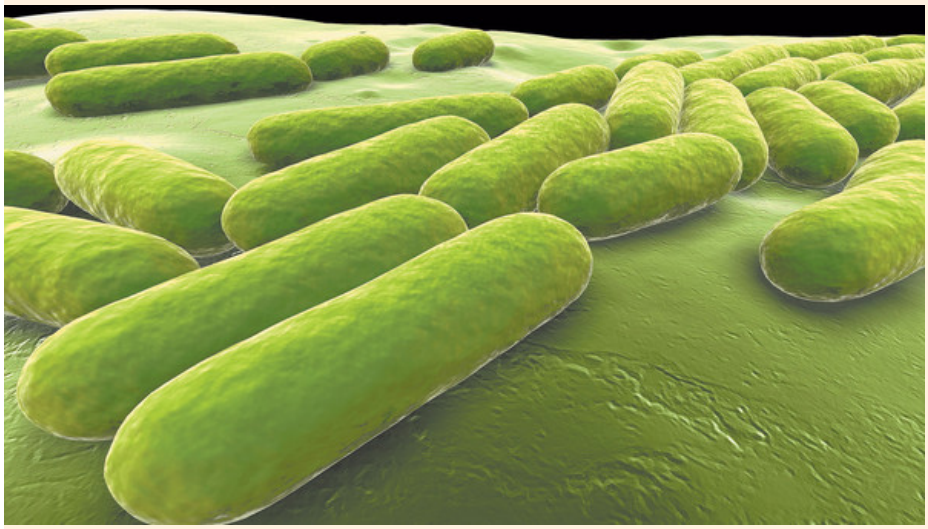
Genetics offers route to cure TB

By Clive Cookson



Breakthroughs: one project is working on an antibiotic to attack the TB bacteria

Around the world, laboratories are working to make up for time lost during the late 20th century, when tuberculosis was ignored or seen as a health problem that had gone away.

Although some of the fruits of this research are already in trials – with 10 drugs in late clinical development and a dozen vaccines in the pipeline – much is still at the earlier stages of scientific investigation.

This month, for example, École Polytechnique Fédérale de Lausanne in Switzerland has set up a charitable foundation to develop what its scientists say is an extremely powerful antibiotic discovered through a European research programme. PBTZ169, as it is known, attacks the TB bacterium *Mycobacterium tuberculosis* through its strong point, the cell wall that shields it from antibiotics and the patient's immune system.

"Our molecule makes the bacterium burst open," says Stewart Cole, director of the Swiss study.

Animal tests show PBTZ169 is very effective when combined with two existing TB drugs, pyrazinamide and bedaquiline. "This could be the winning strategy," says Dr Cole. "These molecules attack different targets in the bacterium. By combining them, we drastically reduce the risk it will mutate into more resistant forms."

Early versions of PBTZ169 were not absorbed fast enough into the body, so the team enlisted new technologies such as structural biology to redesign the molecule. "Tuberculosis is often wrongly considered a disease of the past, but to fight it, we need 21st-century technologies," Dr Cole adds.

The rising power and collapsing cost of genome sequencing are likely to provide important leads to improved TB diagnostics and drugs.

In September, the journal Nature Genetics published papers by four independent research teams on the full DNA sequences of 600 strains of *M. tuberculosis* from around the world. By comparing the genomes, scientists gain insights into the emergence of drug resistance and possible targets for drug development.

For example, China's BGI (formerly Beijing Genomics Institute) discovered 121 genes and mutations strongly associated with drug resistance, which indicated a more complex genetic basis for resistance than previously suspected. "We expect our breakthrough can shed new insights for exploring the mechanisms of drug resistance and lay a solid foundation for protection against TB," says

Dongfang Li, BGI project manager.

Another recent study, published in Lancet Respiratory Medicine, demonstrated the diagnostic potential of DNA sequencing in cases where TB recurs after treatment. Until now, it has been hard for doctors to establish whether a patient has suffered a relapse of the original infection or picked up a new infection with a different strain. Genome sequencing gives the answer, which is important for managing the disease.

“What surprised us in this study is the frequency with which patients were infected with two separate strains of *M. tuberculosis*,” says co-author Stephen Gillespie, professor of medicine at St Andrews University. “As well as being important for TB clinical trials, this has implications for the evolution of multiple drug- resistant tuberculosis.”

Genomics has also shed light on the evolution of TB. Researchers at the Swiss Tropical and Public Health Institute in Basel sequenced the full DNA complement of 259 *M. tuberculosis* strains from around the world and found the bacteria must have moved out of Africa with the first modern humans more than 70,000 years ago and spread round the globe with them.

“The evolutionary paths of humans and TB bacteria show striking similarities,” says Sebastien Gagneux, the study leader. A study of skeletons from a 7,000-year-old site in Hungary by scientists at the University of Szeged found traces of TB proteins and genes in the bones. In parallel with all the genomic analysis, an international project is mapping the molecular circuitry of *M. tuberculosis* – the regulatory networks that adapt to changing conditions in the human body.

“We have generated the first large-scale experimental map of thousands of molecular interactions in the bacterium that enable it to cause disease,” says James Galagan of Boston University, lead author of the project’s report. The study showed, for instance, how TB bacteria cope with a low oxygen environment inside host cells and how they consume human cholesterol.

“Based on this map, we have developed the first computer models that will enable us to study more easily this challenging infectious organism and develop drugs, therapeutics and diagnostics,” Dr Galagan adds.

Molecular and genomic research of this sort will take decades to translate into widely available TB treatments, but it should ensure the pipeline of drugs does not run dry again.