Genome sequence aids war on tuberculosis

Scientists often turn to military metaphors when they describe how the body tries to fend off infectious agents. Immune cells turn into valiant soldiers rallying to a noble cause, while bacteria and viruses become the merciless invading army to be defeated.

In that sense, microbiologists are best viewed as spies studying the enemy to determine its strengths and weaknesses. In the ongoing fight against the bacterium that causes tuberculosis, which claims more lives annually than any other infectious agent, these spies have now collected a long-awaited body of intelligence. In the June 11 NATURE, they unveil the complete DNA sequence of the bacterium's more than 4,000 genes, laying bare all its potential weapons and defenses.

With such information, scientists hope to pinpoint novel targets for drugs. Moreover, by identifying bacterial molecules that trigger immune responses, they may find new leads to vaccines. "The sequence marks a new phase in the battle against one of mankind's most successful predators," writes Douglas B. Young of the Imperial College School of Medicine in London in a commentary accompanying the report on the *Mycobacterium tuberculosis* genome.

Scientists from the Pasteur Institute in Paris and the Sanger Centre in Hinxton, England, spearheaded the sequencing project. They found that the microbial genome consists of more than 4.4 million base pairs, the protein-encoding subunits of DNA.

Unlike many bacteria, *M. tuberculosis* has a complex cell wall, and many of the newly identified genes play a role in creating this protective barrier. One unexpected finding is that the tuberculosis bacterium has more than 250 genes devoted to metabolizing lipid molecules. This suggests that the microbe may obtain much of its energy by digesting lipids of its host, says Stewart T. Cole of the Pasteur Institute.

The researchers have also identified a large number of genes that appear to encode proteins secreted or displayed on the surface of cells. Such proteins may be useful in vaccine development because the immune system responds to them more readily than to the bacterium's internal proteins. Since a vaccine is considered the most likely way to defeat tuberculosis, Cole predicts that investigators will quickly test the vaccine potential of these proteins in animals.

The discovery of two families of novel proteins, whose genes account for about 10 percent of the whole genome, surprised scientists. "This is a huge class of proteins that has been completely overlooked by conventional biochemistry and microbiological approaches," says Cole. "People will be working quite hard to see what they do."

Their resemblance to certain proteins of other bacteria suggests that the newly identified components may help *M. tuberculosis* disarm the immune system. Another possibility, says Cole, is that the newfound proteins enable the bacterium to change its appearance continually and evade detection.

Cole and his colleagues narrowly beat out another group, the Institute for Genomic Research (TIGR) in Rockville, Md., that has also been sequencing *M. tuberculosis*. The TIGR project should be complete in a month, but it will not duplicate the effort of Cole's group, which sequenced a strain of *M. tuberculosis* studied since 1905. TIGR is sequencing a strain recently isolated from a patient. By comparing genomes, scientists hope to understand why some strains spread more easily or initiate disease more quickly.

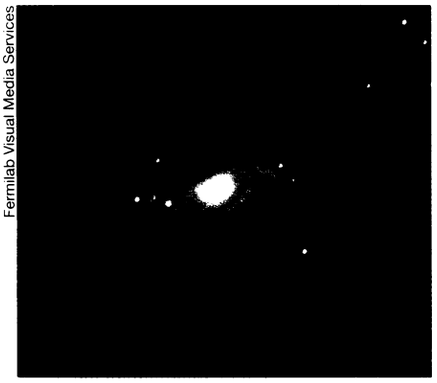
"It's looking like, on average, there's some difference every 5,000 base pairs," says Claire M. Fraser of TIGR. "It's really quite amazing that there are so many [sequence] differences popping up, and I think they will give us some very profound insight into biological differences between strains." —*J. Travis*

Ambitious sky survey gets under way

It took five scientists to unfurl the 30-foot-long segment of the first high-resolution picture taken by the Sloan Digital Sky Survey.

"On behalf of the American Astronomical Society, 'Wow!'" exclaimed the society's president-elect, Robert D. Gerhz of the University of Minnesota in Minneapolis. Researchers displayed the heavenly panorama at a meeting of the society in San Diego this week.

As impressive as that trove of stars and galaxies is, it represents a mere 1 percent of the survey's first detailed image, a 7.5-minute exposure taken on May 27 at Apache Point Observatory near White Sands, N.M. That image, in turn, pales in comparison with what's yet to come.



Fermilab Visual Media Services

The first detailed image from the Sloan sky survey includes a galaxy in the constellation Serpens.

Astronomers expect that when the $77 million Sloan survey is completed, 5 to 7 years from now, it will have generated the first three-dimensional map of the northern celestial hemisphere. The map will include images of 100 million heavenly objects recorded in five colors, along with spectra of the brightest 1 million galaxies and 100,000 quasars. The spectra will yield the redshift, a measure of distance.

Sloan can gauge the distance of galaxies that lie within 2 billion light-years of Earth and of quasars as far away as the edge of the observable universe. Such information will indicate where in the cosmos galaxies and quasars are clustered and where they are relatively scarce.

Researchers conceived the ambitious project a decade ago "to understand how structure in the universe formed from the formless quark soup that existed during the [cosmos'] earliest moments," says team member Michael S. Turner of the University of Chicago and the Fermi National Accelerator Laboratory in Batavia, Ill.

The survey relies on a 2.5-meter telescope and a camera with a foot-long expanse of solid-state light detectors that contain more pixels than the human eye. Rather than scan the sky by slewing to and fro—a time-consuming process—the telescope remains stationary and, as Earth rotates, the sky drifts by.

The flood of data from the survey will constitute "a permanent digital encyclopedia of the sky," says Bruce H. Margon of the University of Washington in Seattle. He asserts that astronomers will soon be able to solve many problems by going to that archive rather than to a telescope.

In a year or two, says Turner, the Sloan survey is likely to have gathered enough data to test cosmological models rigorously. For example, it might provide evidence indicating whether the universe will expand forever or eventually collapse in on itself.

A complementary, but smaller, survey, begun last fall, has measured the distances to some 10,400 galaxies in the southern celestial hemisphere. That survey uses an Australian telescope and plans to take spectra of 250,000 galaxies by 2000. —*R. Cowen*