process, said NHGRI chief Francis Collins, is to turn these preliminary ideas into formal recommendations. The co-chairs are expected to issue a report in the next few months. Collins recommended that over the next few years, NHGRI solicit white papers, hold additional conferences, and support pilot projects to explore the scientific and political questions underlying the choice. Ultimately, said Collins, the institute will issue a call for investigator-initiated proposals, and the decision will be left to the peer-review process. From the looks of things last week, there will be no shortage of applications.

–JOSH GEWOLB

MICROBIOLOGY

S. pneumoniae Genome Falls to Sequencers

At the height of his power, Genghis Khan and his armies swept from the steppes of Mongolia, capturing two-thirds of the known world. But for sheer ferocity, Khan's forces pale next to those of a tiny microbe called *Streptococcus pneumoniae*. These pathogenic bacteria readily move from the throat to invade the lungs, blood, or brain—every year killing millions of children and elderly people worldwide with pneumonia, bloodstream infections, or meningitis. Now, researchers have uncovered clues to just what makes the organism so savage.

On page 498, a team led by Claire Fraser and Hervé Tettelin of The Institute for Genomic Research (TIGR) in Rockville, Maryland, reports the exact order of the 2.16 million bases that make up the genetic code of a virulent *S. pneumoniae* strain. By examining the sequence and comparing it with those of other strains, the team found that the microbe is particularly well equipped to invade the body's tissues. It also seems adept at shuffling its genes—an ability that may help it evade the immune system. This "thrilling view" of the *S. pneumoniae* genome offers "a [new] glimpse into the lifestyle of the organism," says microbiologist Alexander Tomasz of Rockefeller University in New York City.

It should also provide new targets for better drugs to treat *S. pneumoniae* infections and vaccines to prevent them, both of which are badly needed. The microbe's resistance to penicillin and related antibiotics has skyrocketed worldwide in the last decade, and none of the vaccines on the market can ward off all the dangerous strains.

The TIGR team began the sequencing project in 1996, but progress was slowed by a series of technical problems and a split with the institute's original sponsor, Human Genome Sciences of Rockville, Maryland, that caused a temporary funding drought. Although TIGR made most of the raw sequence data available in 1997, the team took several more years to finish the sequencing and characterize the genes, a process called annotation.

Meanwhile, several companies, including Glaxo Wellcome and SmithKline Beecham (now merged to form GlaxoSmithKline) and Eli Lilly & Co., sequenced most of the genomes of three other *S. pneumoniae* strains. GlaxoSmithKline's Damien McDevitt predicts that "there are at least 10 genomes out there from different companies." So far, however, only two have been made public.

A team led by Jose García-Bustos of GlaxoSmithKline's molecular microbiology division in Tres Cantos, Spain, published the annotated but incomplete genome of a virulent, antibiotic-resistant *S. pneumoniae* strain in the June issue of *Microbial Drug Resistance*. After publishing an incomplete draft of the genome of a widely studied, nonvirulent laboratory strain in 1998, an Eli Lilly team says a more complete version is in press at the *Journal of Bacteriology*.

Comparing multiple genomes is key for stopping *S. pneumoniae*, because 92 different strains infect humans—and researchers would like to protect against all of them. The TIGR team has taken a step in that direction by comparing its strain with both a nonvirulent laboratory strain and a second virulent one. This revealed that about 10% of the genes in the virulent TIGR strain are missing in the other two, pointing to several genes that may be important for infection. (In the June issue of *FEMS Microbiology Letters*, microbiologists Gianni Pozzi and Marco Oggionni of the University of Siena Medical School in Italy, who also used TIGR data, reported similar results.)

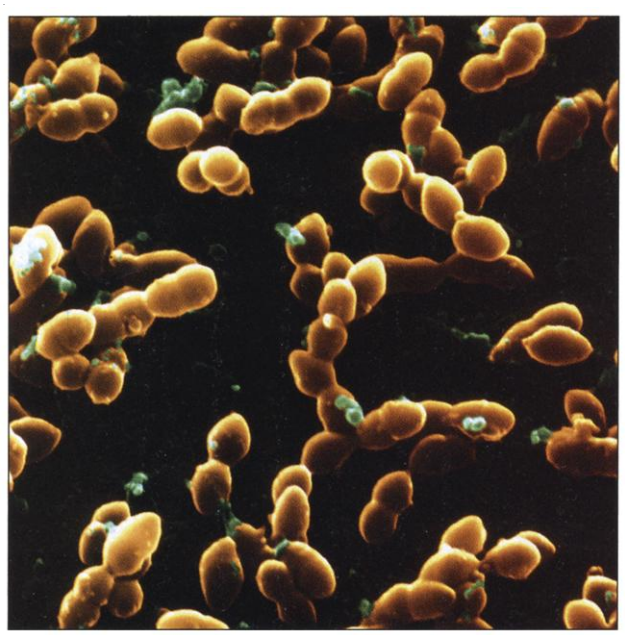
Among the potentially important genes are a group that encodes a variety of unusual cell-surface enzymes that the microbe uses to break down the carbohydrates that help hold biological membranes together, thus weakening barriers to invasion and freeing sugars for the bug to eat. Indeed, *S. pneumoniae* appears to have sworn off many amino acids in favor of sugars. If similar carbohydrate-degrading enzymes are found in all the pathogenic strains, they might be good drug targets or vaccine candidates.

But another finding suggests that *S. pneumoniae* may be more capable than most bacteria of undergoing the genetic changes needed to elude such protective agents. Several of the microbe's genes appear to be foreign—possibly acquired from other bacteria. In addition, 5% of the *S. pneumoniae* genome is made up of small genetic elements that can hop to new locations in the chromosome—compared to 3% or less in more typical bacteria. "That's an incredible number," Tomasz says.

In another departure from the norm, almost all of these so-called insertion sequences had hopped between genes rather than into them. Together, the results suggest an "extraordinary capability to take DNA, move it around, shuffle it, and do it without making any mistakes," says infectious-disease specialist Elaine Tuomanen of St. Jude Children's Research Hospital in Memphis, Tennessee.

Despite the bug's craftiness, experts are optimistic that the genome data will help uncover how the microbe activates key genes as it invades the deep tissues of the body. "It will be like having a frozen picture that all of a sudden starts moving," Tomasz says.

–DAN FERBER



Fearsome invader. Squads of sugar-digesting enzymes may help *Streptococcus pneumoniae* bacteria, such as these, eat their way through human tissue.

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