GENOME RESEARCH

Venter Wins Sequencing Race—Twice

The race to sequence the first complete genome of a free-living organism ended with a flourish last week when Craig Venter, director of The Institute for Genomic Research (TIGR), unveiled the complete sequences of not just one, but two bacteria: *Haemophilus influenzae* and *Mycoplasma genitalium*. Venter made his announcement at a 24 May session of the 95th General Meeting of the American Society of Microbiology (ASM), held in Washington, D.C.

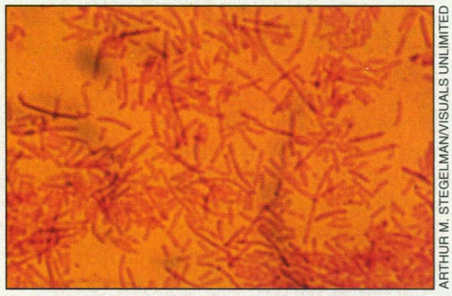
"A remarkable milestone" is how Francis Collins, director of the National Center for Human Genome Research at the National Institutes of Health (NIH), described the accomplishment. Jay Grimes, who heads the Department of Energy's microbial genome project, which funded the sequencing of *M. genitalium*, described himself as "ecstatic."

There is certainly reason for excitement. TIGR's accomplishment—the result of a collaboration with a team led by molecular geneticist Hamilton Smith of Johns Hopkins University in Baltimore who won the Nobel Prize for isolating restriction enzymes from *H. influenzae*—is a landmark for modern genetics. Although the tiny genomes of numerous viruses have already been sequenced, those organisms grow and multiply only with the help of the genetic information contained in the cells they infect. In contrast, the sequences of *H. influenzae* and *M. genitalium* are true genetic blueprints, containing all the information needed to sustain life (*Science*, 13 January, p. 172).

"Everything that should be there for independent life is there," said Venter, who told meeting attendees that a paper describing the effort to sequence *H. influenzae* is under review at *Science*. For example, among the 1749 genes packing the genome of *H. influenzae* (a bacterium that, despite its name, causes ear infection) are those encoding transcription enzymes that copy DNA into RNA and the enzymes that transmute nutrients into usable energy.

As more bacterial genomes are sequenced, researchers will be able to compare them and deduce which genes are responsible for bacterial features such as the ability to cause different diseases and adapt to different environments. And because there are many similarities in bacterial and human biochemistry, the sequences will also be useful for searching for human genes, including those implicated in diseases such as cancer. Bacterial gene sequences have already proved their value in that regard, having helped identify the "mismatch repair" genes that when defective trigger a certain type of colon cancer (*Science*, 10 December 1993, p. 1645).

Over the past few years, TIGR scientists have often been snubbed by public-sector geneticists because they helped generate a massive private database of human gene markers for Human Genome Sciences, the Gaithersburg company that funds TIGR. At the ASM meeting, Venter announced that the whole *H. influenzae* genome sequence will be deposited in public databases at the time of publication. He also took obvious pleasure in noting that NIH had refused to provide federal funds for the effort, because it feared, he said, that TIGR's approach to sequencing the whole genome would fail.



ARTHUR M. STEGELMAN/VISUALS UNLIMITED

Groundbreaking bug. *Haemophilus influenzae*, the first free-living organism to be sequenced.

Until now, the favored course for sequencing genomes has been to carefully break the DNA into ordered, overlapping segments—an extremely time-consuming task—and then sequence the pieces and reassemble them. But Venter and Smith took a more novel approach called whole-genome shotgun sequencing. They simply shattered *H. influenzae* genomes with ultrasonic waves to create DNA fragments whose order was unknown. They then sequenced the fragments and, using powerful computers, put them in order according to how their sequences overlap.

Even as they were sequencing *H. influenzae*, the TIGR-Hopkins team realized, said Venter, that "if we do it again, we can do it much better." After revving up the computer software so that it could process more information, the Venter-Smith collaboration went on to sequence the complete genome of *M. genitalium*, a simple bacterium associated with reproductive tract infections, in less than 4 months.

Despite the excitement generated by the completion of the first full genomic sequence of a free-living organism, such accomplishments may soon seem mundane—at least if TIGR has its way. The institute has the capacity to complete "10 or more microbial genomes per year with high efficiency," Venter told meeting attendees.

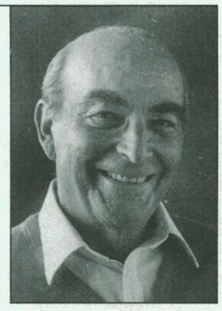
–Rachel Nowak

BIOTECH PATENTS

Scientists Named in PCR Suit

If your lab uses the polymerase chain reaction (PCR), your name may have come up in a San Francisco court. The Swiss pharmaceutical company Hoffmann-LaRoche recently gave the court a list of about 200 basic researchers who—so the company claims—are infringing on its patent for Taq polymerase, the enzyme used in PCR to amplify DNA. Those on the list haven't been charged with patent infringement or anything else. But they are being used by both sides as pawns in a legal battle between Roche and Promega Corp. of Madison, Wisconsin, over Promega's license to sell Taq.

The legal fireworks began after Roche bought the PCR-related patents from the now-defunct Cetus Corp. in late 1991. Cetus had, through those patents, licensed Promega and several other companies to sell Taq for non-PCR uses, such as DNA sequencing. Those companies agreed to refrain from promoting their Taq for PCR. But in October 1992, Roche sued Promega, claiming that the company's marketing and packaging of the enzyme encourages its use in PCR (*Science*, 4 December 1992, p. 1572). Promega denied wrongdoing and responded with its own lawsuit challenging the validity of the Taq patent (*Science*, 23 April 1993, p. 486). Both suits have slowly been working their way through federal courts in New Jersey and San Francisco, with no end in sight.



Opposes PCR patent. Arthur Kornberg.

Because "Roche accused us of contributing to and inducing infringement of their patents," says Promega President William Linton, "we simply asked the question, who are the direct infringers?" Roche was legally obliged to produce this list for the case to go forward. So, according to Kathy Ordoñez, president of Roche Molecular Systems in Branchburg, New Jersey, Roche scanned the literature for publications that mentioned PCR, searched the materials and methods sections for the source of the Taq polymerase, and listed authors who named Promega as their source of Taq. Roche submitted the list to the court 2 weeks ago.

Linton submitted it to assembled journalists at a San Francisco press conference a week later. He says basic researchers should be alarmed by the list, which he cites as evi-