Chlamydia bacterium yields surprise genome

The bacterium responsible for chlamydia, the most common sexually transmitted bacterial disease in the United States and the leading cause of preventable blindness worldwide, has now surrendered the genetic secrets that may one day bring about its destruction. In the Oct. 23 SCIENCE, the nearly 900 genes of *Chlamydia trachomatis* make their debut, thanks to a research group led by Richard S. Stephens of the University of California, Berkeley.

Not surprisingly, scientists are thrilled at the unveiling of the genome for this microbe, which lives only inside other cells.

"It's going to tremendously facilitate, as well as stimulate, research," says Thomas P. Hatch of the University of Tennessee in Memphis.

"It's like we were working in a room with the lights turned out, and now someone has turned them on," agrees Robert C. Brunham of the University of Manitoba in Winnipeg. "One of the most striking things to me is that we had concocted [the view] that chlamydia was a very strange microorganism, but the genome information shows us that it's very much like any other bacterium."

For example, its genome contains all the genes needed to synthesize ATP, the energy-storage molecule used by most organisms. Because scientists had previously regarded *C. trachomatis* as an "energy parasite" that steals ATP from its host cell, finding that the bacterium can probably generate the molecule has startled researchers.

The genome may also resolve the so-called penicillin paradox. This antibiotic, which targets a common bacterial cell wall component known as peptidoglycan, works on *C. trachomatis* even though the bacterium wasn't thought to use the molecule. The new results, however, reveal that all the genes required to make peptidoglycans are available.

Many of the misconceptions about *C. trachomatis* have arisen because scientists have not been able to grow and study it in isolation. "Chlamydia biology and biochemistry are shrouded in mystery," says Hatch.

"It was always very difficult to decide what was going on in chlamydia and what was going on in the host cell," adds Brunham.

While having the chlamydia genome won't necessarily give scientists the ability to grow the bacterium, the knowledge has brought new insights. Scientists had previously identified just a single surface protein for the bacterium. The genome reveals several more.

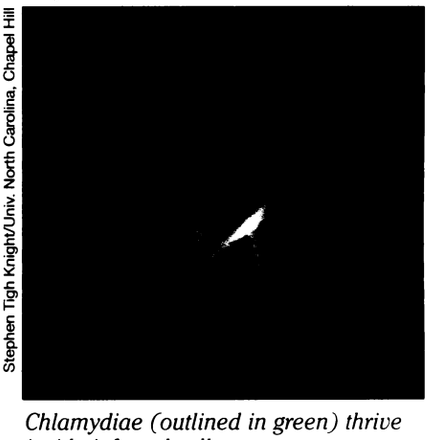
"There's a whole new family of surface proteins we didn't know about, which definitely could be very important in developing a vaccine," says Brunham. He has been experimenting with DNA vaccines, which rely on the idea that the gene for a protein, rather than the protein itself, can stimulate an immune response (SN: 5/11/96, p. 302).

Scientists are puzzled by an absence of some genes thought essential to bacteria. In particular, a gene called *FstZ* drives cell division in all other known, bacterialike microbes. It's unclear how *C. trachomatis* can reproduce without it.

From an evolutionary perspective, as well, the new genome is a treasure chest. The bacterium possesses at least 20 genes that it has apparently borrowed from host cells over the years; other bacterial genomes have only 3 or 4. The appropriated genes most closely resemble plant genes, suggesting that *C. trachomatis* originally infected an ancient plantlike organism. The sheer number of stolen genes also implies that the bacterium has made a home inside cells for eons, note Stephens and his colleagues.

"A case can be made that chlamydia may have gone intracellular a long, long time ago . . . . [It] may have indeed done it before multicellular organisms existed," says Hatch.

Researchers should gain an even better perspective on the evolution of *C. trachomatis* once they complete the genome of *Chlamydia pneumonia*, a related bacterium that causes pneumonia and may trigger atherosclerosis (SN: 6/14/97, p. 375). —*J. Travis*



Stephen Tigh Knight/Univ. North Carolina, Chapel Hill

Chlamydiae (outlined in green) thrive inside infected cells.

Making use of mismatched donor marrow

To beat leukemia, it helps to be lucky. A bone marrow transplant can give a patient a fresh start at producing blood cells free of this cancer, but a successful transplant typically requires that at least five out of six key genetic markers in the donor match those in the recipient.

Unfortunately, most patients don't find a good match even among close relatives willing to donate bone marrow and must hope to get appropriate bone marrow from a tissue bank. Some wait months for a good match, and others die waiting. Some acutely ill patients, having little choice, must accept the best available transplant—blood in which only three or four of the six markers are correct. Having a mismatched donor worsens the recipient's survival odds because the transplanted tissue is often rejected.

A study in the Oct. 22 NEW ENGLAND JOURNAL OF MEDICINE brightens the picture for leukemia patients. By giving them a massive dose of stem cells—the marrow cells that harbor blueprints for new, healthy blood cells—researchers in Israel and Italy find they can overwhelm a recipient's remaining immune cells and thwart rejection. The dose of stem cells, collected from blood instead of bone marrow, is up to 10 times greater than a marrow transplant would normally provide.

Even when the donated stem cells are mismatched for three of the six markers, the survival rate of recipients approaches that of patients receiving blood from well-matched, unrelated donors.

In both the marrow and new stem-cell transplant procedures, patients typically receive radiation treatment, chemotherapy, and drugs to suppress immune rejection and ward off disease. Even so, the patients can encounter a cancer recurrence, infection, transplant rejection, or graft-versus-host disease, in which the donor's immune cells attack the patient.

The researchers extracted stem cells from the blood of donors who had been primed with hormones to produce these cells prodigiously. To lessen the risk of graft-versus-host disease, the technique also removes the donor's immune T cells.

Of 43 terminally ill leukemia patients treated with this procedure, 12 survived and were healthy 18 months after the stem-cell transplant, says study coauthor Yair Reisner of the Weizmann Institute in Rehovot, Israel. The other patients died or suffered a relapse of leukemia.

"For patients who don't have matched donors or don't have time to wait, this is a huge step forward," says LeeAnn T. Jensen of the National Heart, Lung, and Blood Institute in Bethesda, Md.

At the core of the mismatch problem are human leukocyte antigens, cell-surface proteins that help direct immune system functions. Genes encoding these proteins are inherited as a unit, one from each parent. Identifying the DNA sequence at three specific locations on each unit provides the six genetic markers used in seeking a match.

Less than a third of patients have a family member who matches five or six markers, but everyone's parents and most siblings match at least three. "It would be very unusual that you wouldn't have a [related] donor for every patient," Reisner says. —*N. Seppa*