Obscure Drugs Cure Malaria in Mice

The high-tech drudge work of sequencing genes is starting to pay dividends. Using newly discovered genetic clues about a parasite that causes malaria, scientists in Germany have cured the disease in mice with two drugs previously used to combat bacterial infections in people. The finding suggests these drugs might successfully treat people who have malaria.

The most severe cases of the disease stem from *Plasmodium falciparum*, the single-cell parasite that has been on scientists' hit list since they first discovered malaria was carried by mosquitoes. For the past century, *P. falciparum* has withstood the best scientific weaponry, ranging from quinine to synthetic vaccines.

The new approach exploits a molecular chainreaction that ultimately produces isoprenoid compounds, which organisms need to survive. This construction process, or pathway, relies on specific enzymes that facilitate each step in the synthesis of isoprenoids.

Scientists have been looking for an isoprenoid pathway in malaria parasites. However, it has become clear in recent years that the pathway used by animals and plants is missing in *P. falciparum*. Some algae, bacteria, and plants, however, make isoprenoids by employing another set of enzymes.

The researchers in Germany sought such a pathway in *P. falciparum* by plowing through its genome. There, they found genes that encode two components in the isoprenoid pathway used by algae, bacteria, and plants, says study coauthor Jochen Wiesner, a physician and biologist at Justus Liebig University in Giessen, Germany. These enzymes are DOXP synthase and DOXP reductoisomerase.

Meanwhile, other research has shown that a little-known antibiotic destroys DOXP reductoisomerase. The drug, called fosmidomycin, was first synthesized by Fujisawa Pharmaceuticals of Japan. For Wiesner and his colleagues, the drug and its derivative, FR900098, became obvious candidates for weapons against the parasite's pathway.

Tests against *P. falciparum* in laboratory dishes showed that shutting down the pathway with the antibiotics kills the parasite, the researchers report in the Sept. 3 SCIENCE.

Because *P. falciparum* grows only in primates, the team infected several groups of mice with the parasite *Plasmodium vinckei*, which causes lethal malaria in mice. The mice were then given FR900098 or fosmidomycin. Moderate doses of either drug cured the mice outright in 8 days, whereas untreated mice died of malaria within that time.

Mice receiving the drugs orally needed greater doses to achieve the same effect that an injection provided. Nevertheless, "these were still safe amounts," Wiesner says.

Whether fosmidomycin or its derivative will kill *P. falciparum* in a person remains unproved. The researchers don't know if the parasite, once it has infected a red blood cell, relies exclusively on the DOXP pathway to manufacture isoprenoid compounds.

There's no evidence that the alternative pathway in animals and plants exists in *P. falciparum*, says study coauthor Hassan Jomaa, a physician at Justus Liebig University. "Whether these isoprenoids are synthesized de novo by the parasite or taken from the [host] medium is not yet definitively proven," Jomaa notes. "However, our data suggest that at least some essential isoprenoids are synthesized de novo."

"Sole dependence on the DOXP pathway would probably raise the value of this pathway's enzymes as drug targets," says Robert G. Ridley of the World Health Organization in Geneva, writing in the same issue of SCIENCE.

This mouse study "shows that the malaria genome project is bearing fruit," says Stephen L. Hoffman of the Naval Medical Research Center in Bethesda, Md. He is a participant in the international consortium that has been sequencing the *P. falciparum* genome and posting completed portions on the Internet for researchers, such as the German team, to use.

"We hoped to promote this exact type of finding," Hoffman says.

Wiesner says that the scientists are prepared to test the drugs on malaria patients because the toxicological data on fosmidomycin already indicate that it's safe to use. In fact, the data suggest that effective doses would be less than the amounts that physicians would prescribe to fight bacterial infections. —*N. Seppa*

Keen-sighted X-ray telescope debuts

Astronomers have started peering through a newly launched X-ray telescope with spectacular results. The $1.5 billion Chandra X-Ray Observatory, formerly known as the Advanced X-Ray Astrophysics Facility (SN: 1/3/98, p. 8), resolves details approximately 10 times finer and detects sources 20 to 50 times fainter than its predecessors could.

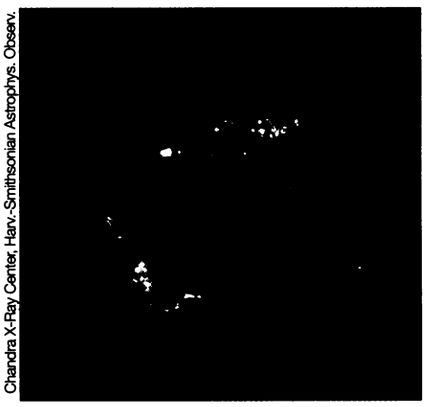
In tests of one of its X-ray cameras, the 14-meter-long, 4.6-ton satellite made brief exposures that boast extraordinary detail. The pictures unveil previously hidden features of a supernova remnant near the constellation Cassiopeia and a jet of radiation 6 billion light years away from Earth.

On Aug. 28, scientists first tested one of Chandra's gratings, similar to prisms, for spreading radiation into a spectrum of lines. The telescope was focused on Capella, a binary star some 40 light years away. The trial revealed a forest of distinct marks where previous X-ray spectra showed only a blur.

The instrument, named after the late Nobel laureate Subrahmanyan Chandrasekhar (SN: 1/18/97, p. 39), will have a tremendous impact on astronomy, predicts Harvey D. Tananbaum, who directs the Chandra X-Ray Center in Cambridge, Mass. "You will be able to pick out things you haven't seen before," he says, such as stars forming in central galaxies of galactic clusters.

Astronomers have been waiting for Chandra for a long time: Tananbaum and others proposed the project in 1976. "When you've been waiting 15 years for Christmas, it had better be very good," says Richard F. Mushotzky of NASA's Goddard Space Flight Center in Greenbelt, Md., who joined the project's science oversight board in 1984.

"I think we're going to have a very good Christmas," he predicts. —*P. Weiss*



Chandra X-Ray Center, Harv.-Smithsonian Astrophys. Observ.

Fiery gas, spewing X-rays, hurtles outward from the suspected explosion, or supernova, of a massive star. The unprecedented visual acuity of NASA's Chandra X-Ray Observatory may have allowed it to spot a long-sought neutron star or black hole (center yellow-orange dot) at the heart of this 28-million-kelvin gas bubble known as Cassiopeia A.