MedicalXpress

Novel class of antibiotics shows promise against plague, drug-resistant bacteria

July 25 2017

Pathogenic bacteria are rapidly developing resistance to the arsenal of microbial therapies—and driving researchers to identify families of therapeutics with new modes of action. Recently, those include antibiotics that inhibit LpxC, an enzyme critical to forming the outer membrane of Gram-negative bacteria. This week in *mBio*, an international group of scientists report on laboratory experiments suggesting that a novel LpxC inhibitor can treat multi-drug resistant bacterial infections, including many that originate in hospitals.

The new drug, LPC-069, also proved an effective treatment, in mice, for infection by *Yersinia pestis*, the Gram-negative bacteria that causes bubonic plague. The disease is fatal if not treated and diagnosed in over 1,000 people annually.

LpxC inhibitors represent a new class of antibiotics that might treat a raft of infectious diseases caused by Gram-negative microbes. Biologists first suggested targeting LpxC as a treatment strategy more than 20 years ago, but researchers were unable to identify a compound that was safe at effective dosage levels, says biochemist and structural biologist Pei Zhou at Duke University in Durham, North Carolina.

"Our study shows that LpxC is a viable target, and we can dose the compound (LPC-069) at very high levels without noticeable toxicity," says Zhou, who co-led the study with biologist Florent Sebbane, a researcher at the French National Institute of Health and Medical Research (Inserm) who works at the Pasteur Institute of Lille, France.

Development of the drug was led by Pei Zhou and chemist Eric Toone, also at Duke University.

Zhou, Toone, and Sebbane reported on another LpxC inhibitor, called LPC-058, in the current and previous studies, that demonstrated antibiotic activity in vitro. LPC-058 also delayed plague infections in mice; however, the compound led to side effects including diarrhea, the accumulation of white blood cells in the lungs and intestines, and, at the highest doses, liver toxicity.

LPC-069, on the other hand, caused no serious side effects at any of the tested doses, including the highest dose, the researchers reported. In vivo studies of the compound showed antibiotic activity against more than a dozen pathogenic bacterial taxa, including multi-drug resistant clinical strains. Except for the plague-causing *Y. pestis*, all the bacteria were cultured from patients at the Lille University Hospital in Lille, France.

To test the efficacy of the compound against plague, the researchers injected 15 mice with *Y. pestis*. Animals in the control group received no treatment. Eighteen hours after infection, mice in the experimental group received treatment with high-dosage LPC-069. Five days later, the untreated mice were dead, and mice treated with LPC-069 survived. Autopsies conducted two weeks after treatment showed no signs of *Y. pestis* organ colonization in the experimental group, suggesting a successful cure of infection.

LpxC is one of the six essential enzymes in the lipid A (Raetz) pathway in Gram-negative bacteria, and Zhou suspects that others essential lipid A enzymes might be valuable targets for antibiotic treatment as well.

Sebbane says researchers need to test the drug's efficacy against drug-resistant infections in animals. The researchers are also exploring the drug's effectiveness against the full range of Gram-negative infections,

including strains that are resistant to commercially-available antibiotics.

Provided by American Society for Microbiology