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A Plague On Many Houses

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Description

During its life cycle, Y. pestis, the infamous “Black Death” bacteria must survive the “bio” environment of a flea in order to explode in the vastly different human system. A team turned advanced robotic high-throughput technologies on Y. pestis, looking for weaknesses in this highly adaptable killer.

Newswise — Yersinia pestis, the causative agent of the “Black Death” or “Bubonic” plague, has been a scourge of human civilization. One of the most virulent bacterial pathogens known, killing nearly 90% of those infected, Y. pestis was responsible for three historic pandemics that shattered whole societies. And plague is still with us. In Madagascar, a naturally antibiotic-resistant strain of plague erupted in the 1990s. In western North America, Y. pestis lurks in wild rodent populations. Throughout the world, there is new fear of Y. pestis as a bioterror agent.

Now a new and revealing portrait of this old nemesis is emerging from Lawrence Livermore National Laboratory. Scientists using advanced robotic high-throughput technologies have completed what is believed to be one of the most comprehensive and rapid studies ever of how growth conditions affect the virulence of a deadly bacterium. Ann E. Holtz who works in the laboratory of Sandra McCutchen-Maloney used a battery of phenotype array machines, pre-loaded 96-well plates, and robotic observers to chart the effects of 2,000 nutrients and chemicals, including about 240 different antibiotics, on the viability of Y. pestis under four separate, physiologically relevant growth conditions. Traditional studies of pathogens examined one to two dozen parameters under one or two growth conditions. In contrast the new technologies allowed Livermore researchers, in effect, to conduct 8,000 experiments in about a week.

The picture drawn by Holtz from her high-throughput data shows Y. pestis to be even tougher than suspected under conditions that mimic its life outside the human host, and possibly less vulnerable under human infection conditions to antibiotics currently used to treat plague, such as kanamycin, doxycycline and tetracycline. The researchers caution that these results are preliminary and will require further tests.

High (e.g., human body) temperatures and low calcium levels were known to trigger the virulence of Y.

pestis. However an evolutionary challenge for the deadly bacterium is to survive in the hostile biological “climate” of its carrier host, the flea, until it can be transmitted through a fleabite to one of its favorite reproductive hosts, Homo sapiens. Even in the human bloodstream, the bacterium curbs its virulence until it can interact with a target cell where conditions are right to finally unleash its killing powers. Holtz used four conditions as models that mimic the biological conditions when Y. pestis is: (1) located in the flea (low temperature [26º C], high calcium); (2) located in the human bloodstream (high temperature [37º C], high calcium); and (3) interacting with a human cell (high temperature [37º C], low calcium). The fourth condition, low temperature [26º C] and low calcium, was included as a control for full comparison. To see how Y. pestis fared in each condition, microarray wells pre-loaded with each of 2,000 different chemicals were infected with the bacterium and incubated with a marker dye to measure growth. Each well was monitored every 15 minutes for three days by an “Omnilog” robot.

As expected, Y. pestis flourished at the high-temperature, low-calcium growth conditions found inside mammalian cells. The bacterium also had increased resistance to antibiotics in flea-like conditions (low-temperature, high-calcium). Strikingly, at these lower temperatures, the bacterium also resisted many osmotic stressors—salt, phosphates, and urea—that killed it at higher temperatures.

We’ve always known that the plague-causing bacterium is a formidable enemy, say the Livermore researchers. This new high-throughput format now allows us to study it and other bacterial pathogens in greater depth, under wider conditions and with more speed than ever before. These are encouraging findings, and will help researchers rapidly screen for optimal ways to kill pathogens under human infection conditions.

Metabolic Differences in Yersinia pestis as a Function of Temperature And Calcium Detected by Phenotype Array, A. E. Holtz,1 I. K. Fodor,2 J. P. Fitch,3 S. L. McCutchen-Maloney1 ; 1 Biodefense Division, Lawrence Livermore National Laboratory, Livermore, CA, 2 Center for Applied Scientific Computing, Lawrence Livermore National Laboratory, Livermore, CA, 3 Chemical and Biological National Security Program, Lawrence Livermore National Laboratory, Livermore, CA. This work was performed under the auspices of the U.S. Department of Energy by the University of California Lawrence Livermore National Laboratory under contract No. W-7405-ENG-48 with support from the Department of Homeland Security. UCRL-ABS-205617

At the ASCB Meeting: Session 438 Host-Parasite Interactions, Poster Presentation 2564, Halls D/E. Author presents: Wednesday, Dec. 8, 1:30 —3:00 PM.
