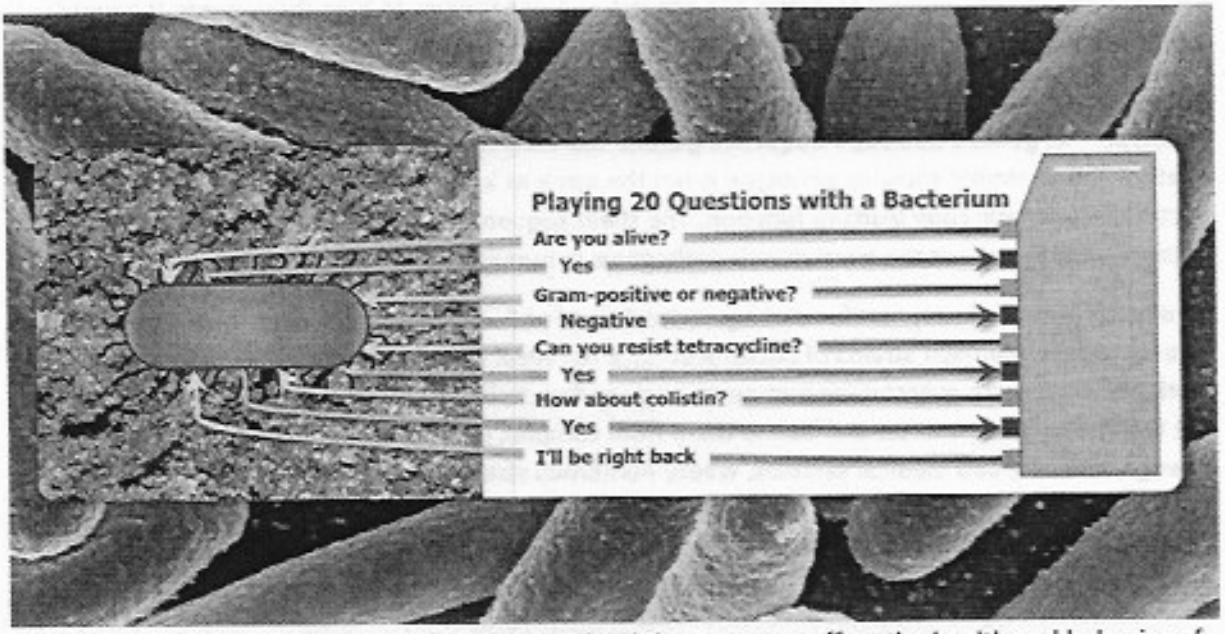
**Playing 20 Questions with Bacteria to Distinguish Harmless Organisms from Pathogens**

**New biosurveillance technology would quickly identify potentially harmful traits in unfamiliar bacterial strains**

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Bacteria underpins much of our world, acting behind the scenes to affect the health and behavior of animals and plants. They help produce food, provide oxygen, and even reshape the environment through a vast array of biological processes. They come in a phenomenal number of strains—many still unknown—and thrive in different ecological and environmental niches all over the world. But while their diverse behaviors makes them essential to life, bacteria can also be deadly. This threat only grows as greater global travel brings people into contact with new places, foods, and animals, dramatically increasing the chances of exposure to dangerous microbial species known as pathogens.

How can the Department of Defense—whose forces, deployed around the world, constantly come into contact with new bacteria—discriminate between harmless and virulent strains to prevent a disease outbreak that threatens military readiness? Friend or Foe, a new program from DARPA's Biological Technologies Office, proposes to develop a platform technology that rapidly screens unfamiliar bacteria to establish their pathogenicity and even discover unknown pathogenic traits, necessary first steps for designing effective biosurveillance and countermeasures.

"Trends such as rising global population, changes in the environment, and the growing accessibility of tools for genetic engineering mean that our armed forces are increasingly likely to face new bacterial pathogens, whether they occur naturally or are engineered by adversaries," said Paul Sheehan, the program manager for Friend or Foe. "Our existing biosurveillance strategies don't work on previously undiscovered bacteria or on bacteria that have been specifically designed to evade detection by current tests. We need new screening tools that can quickly characterize the threat to enable a rapid response."

Existing forensic technologies for identifying bacteria are limited in their application and fall primarily into two categories: rapid diagnostic microbiology, which is confined to approximately 350 known strains and requires cultured bacteria; and metagenomics, which only inventories previously known

bacteria present in a sample. Both technologies take 36 hours or longer to deliver results, and neither is capable of quickly evaluating previously unknown bacteria, especially strains that cannot be cultured in a laboratory. This means that, at present, the vast majority of bacteria species cannot be readily evaluated for risk to humans.

Yet within this diversity of bacteria—at least $10^7$ to $10^9$ species—there lies a large pool of unknown traits that could contribute to future pathogenicity. And, since bacteria can transfer traits between species fairly rapidly, individual strains can acquire new capabilities to help them evade the body's innate immune response or to resist antibiotics.

Although new genetic sequencing tools are being developed that can quickly read a bacterium's *genotype*—its genetic makeup—sequencing alone will unlikely solve the challenge of assessing risk. That's because simply knowing genotype is not the same as knowing *phenotype*—how that bacterium's genetic code leads to function. The sheer sequence of a bacterial genome does not indicate whether or not the bacterium is pathogenic in humans.

To directly and efficiently test for pathogenicity, Friend or Foe aims to build a portable platform that screens many unfamiliar strains of bacteria at once to reveal their phenotypes. Developing such a platform will require overcoming numerous engineering challenges. First, without killing the bacteria, the technology must extract and isolate them from complex environments such as soil, runoff, sewage, biofilms, and medical samples, where numerous strains of bacteria live together. Second, the system must sustain the bacteria in simulated host environments long enough to conduct testing. And third, it must run and evaluate a gauntlet of physical and chemical tests on the bacteria—the biological equivalent of the game "Twenty Questions"—to determine their pathogenicity.

The Friend or Foe system will test for three traits of pathogenicity. First, can the bacteria survive and establish a niche in a host organism? Does it, for instance, adhere to the host's cell membranes? Second, can the bacteria harm its host? For example, does it secrete toxins or have flagella that could disrupt the host's mucosal tissue? And third, can the bacterium protect itself? Does it inactivate the host's protective antibodies or resist antibiotics?

Dangerous bacteria would be flagged for genetic sequencing to map the newly discovered pathogenic trait to specific genes, leading to simpler biochemical tests for that pathogen in the future. A side benefit of the program would be speeding up all future efforts to identify new bacterial traits and the genes that provide them, which would support research ranging from antibiotic production to the degradation of pollutants.

"There are millions of species of unidentified bacteria in the world, and we now have no quick way of knowing which of those might endanger our troops," Sheehan said. "If we're successful in creating a tool for rapid evaluation of bacterial phenotype, we'll deliver the Defense Department a powerful new capability for force protection and a powerful deterrent to the development of engineered bio-threats."

DARPA envisions Friend or Foe as a four-year, fundamental research program. Once the program begins, a separate independent verification and validation (IV&V) team contracted by DARPA will work with performer teams to provide standardized biological samples that simulate different environments and include mixtures of known bacteria. The IV&V team will also evaluate the effectiveness of the performers' systems following demonstrations.

Researchers supporting Friend or Foe must adhere to all applicable guidelines for biosecurity. DARPA has structured the program so that potential discovery of new pathogens can only take place under the guidance and supervision of federal agencies tasked with preventing the spread of disease.

DARPA will host a Proposers Day on Wednesday, February 28, 2018, at the DARPA Conference Center in Arlington, Virginia. More information is available at https://go.usa.gov/xns5u.

Full details will be made available in a forthcoming Broad Agency Announcement.

***Image Caption:*** *The potential threats posed by unfamiliar bacteria can evade state-of-the-art forensics technology, which requires existing knowledge of a bacterium's function or biochemical makeup. DARPA's new Friend or Foe program aims to develop a platform technology that rapidly screens unfamiliar bacteria to establish their pathogenicity and even discover unknown pathogenic traits, necessary first steps for designing effective biosurveillance and countermeasures.*

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