New route to identify drugs that can fight bacterial infections

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About 100 drugs already approved by the U.S. Food and Drug Administration (FDA) for other purposes can also prevent the growth of certain bacterial pathogens inside human cells, including those that cause Legionnaires' disease, brucellosis, and Mediterranean spotted fever. The findings, published in *mBio*, the online open-access journal of the American Society for Microbiology, demonstrate a new way of identifying non-antibiotic drugs that could one day help curb bacterial infections.

A handful of drugs on the list inhibit the growth of at least three of the four bacterial organisms tested. Those drugs include familiar compounds like loperamide, an antidiarrheal medication sold under the brand name Imodium® and clemastine, an allergy medicine sold as Tavist®, as well as drugs used to treat high blood pressure and angina.

Howard Shuman, professor of microbiology at the University of Chicago and a senior author on the study cautions that this study only looked at infection in the laboratory dish and therefore whether the drugs would effectively treat infections in humans is not known. The work, he says, is a good first step showing this method can identify FDA-approved drugs that might potentially act alongside traditional antibiotics.

"Antibiotic therapy is becoming more difficult to achieve, so looking for alternatives is always a good thing to do," Shuman says.

Shuman and his colleagues thought that certain types of bacteria—those

that infect human cells and then replicate inside those cells—might be vulnerable to other drug approaches.

"Intracellular bacteria resemble viruses in that they need host cell functions to complete their life cycle," says Shuman. So the researchers screened drugs to look for compounds that interfered with those cellular processes. They chose a panel of 640 FDA-approved drugs that have known safety and side effect profiles.

The researchers measured each drug's ability to disrupt the intracellular growth of four bacterial strains: *Coxiella burnetii* (which causes Q fever), *Legionella pneumophila* (Legionnaires' disease), *Brucella abortus* (brucellosis), and *Rickettsia conorii* (Mediterranean spotted fever). Although none of these organisms have become problem infections in the U.S. due to antibiotic resistance, brucellosis and Q fever can both cause chronic and ultimately fatal disease in about 5% of those infected.

The team screened each drug for its ability to reduce intracellular bacterial growth by 80% or more inside human THP-1 macrophage-like immune cells. They eliminated drugs from the list that simply killed off the human host cells or that were known antibiotic or antiviral drugs and identified 101 drugs that presumably disrupt key cellular functions in the host cells.

Shuman's lab group did the experiments on *C. brunetii* and *L. pneumophila*, while Sean Crosson's group at University of Chicago carried out the *B. abortus* work, and Juan Martinez's group, now at Louisiana State University in Baton Rouge, performed the *R. conorii* studies. The work, which was done at the Howard T. Ricketts Laboratory, a biocontainment laboratory operated by the University of Chicago in Lemont, Illinois, shows that known drugs that interfere with host cell properties can stall intracellular bacterial infections.

"There are emerging infections of all sorts—bacteria, viruses, parasites. Working up a new therapy for such things take time," says Shuman. "If we have drugs X, Y, or Z to interfere with host cell functions to slow or impede an infection, then we can have something already on hand to attack it."

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