

A New Approach for a “Post Antibiotic” Era

Problem: a serious lack of new antibiotics

The pipeline for new and effective antibiotics to keep up with ever increasing resistance seems to be running dry. Due to the scarcity of new “silver bullets” that attack bacteria directly, new approaches are being investigated for the so-called “post antibiotic” era.

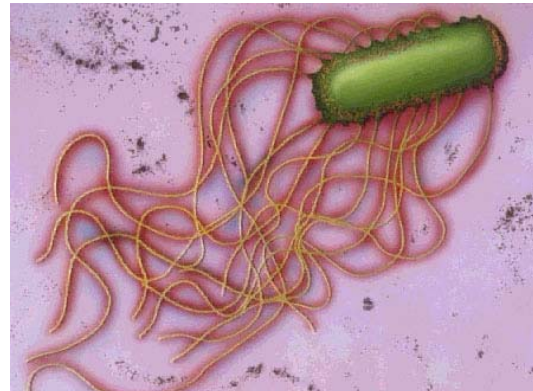
A new class of hormone blocking drugs

The University of Texas Southwestern Medical Center in Dallas is leading the development of a new drug that will block the pathogenic bacteria’s ability to detect human hormones that are necessary for the development of toxin production and disease progression.

The new drug - dubbed LED209 - prevents bacteria from detecting two hormones key for mounting an infection, epinephrine and norepinephrine (also known as adrenalin and noradrenalin). Without these signals, pathogens such as *E. coli* 0157:H7 can't churn out toxins or infiltrate animal cells.

Promising results with animal experiments

When the research team exposed mice to *E. coli* 0157:H7 or Salmonella, rodents that received the drug before infection fared far better than mice that received no antibiotics. More animals survived, and researchers found fewer bacteria in their organs.



E. coli 0157, Salmonella (in photo), and other gram negative pathogens utilize human neurotransmitters to induce toxin production. New drugs are being developed to block these pathways.

In mice infected with tularaemia - a potential bioterrorism weapon that kills mice and humans - LED209 blocked disease progression when the researchers administered the drug several hours after infection. Four-fifths of the animals survived tularaemia, whereas just 10% of the untreated mice pulled through.

The drug should also fend off a wide range of bacterial killers. LED209 targets a protein called QseC. Bacteria that cause pneumonia, bubonic plague and several plant diseases have versions of QseC similar to *E. coli*'s, suggesting that the new drug will hamper them as well.

Resistance proof?

LED209 doesn't kill bacteria. The one bug in a billion that's lucky enough to be resistant to the drug won't get much of a growth advantage since it will have to compete with the overwhelming population of non-resistant strains. This offers a tremendous advantage over today's vulnerable antibiotics.

Cautiously entering the "Post Antibiotic Era"

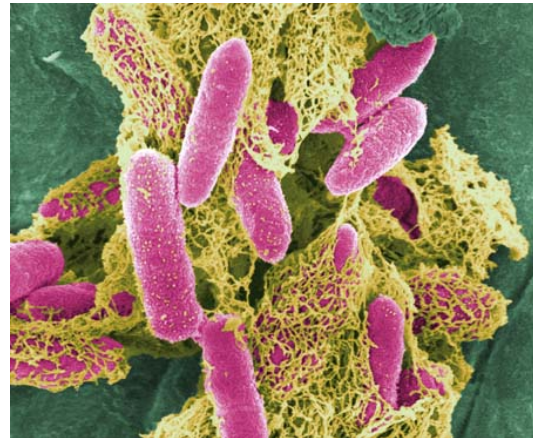
"It's an encouraging direction they're going in," says John Mekalanos, a microbiologist at Harvard Medical School in Boston.

However, any test in humans is at least 5 years off, and the actual wait will depend on how the drug fairs in further animal studies, as well as how safe it is. Early indications in mice hint at few side effects.

Combo therapy may be best

Unfortunately, drug resistance might still be possible, as time and time again, bacteria have proved smarter than man-made drugs. "You could slowly build up more and more resistance in the population in a natural setting," he says.

If LED209 makes it to the clinic, it could work best when paired with a more traditional antibiotic that kills bacteria, Mekalanos says. "Try to hit the bug with two punches."



Electron micrograph of E. coli O157. New strategies for control of infectious diseases are needed that will not induce resistance as seen with today's antimicrobials.

Journal reference: Science (DOI: 10.1126/science.1160354)