MedicalXpress

New tool may allow doctors to 'see' bacterial infection in the body

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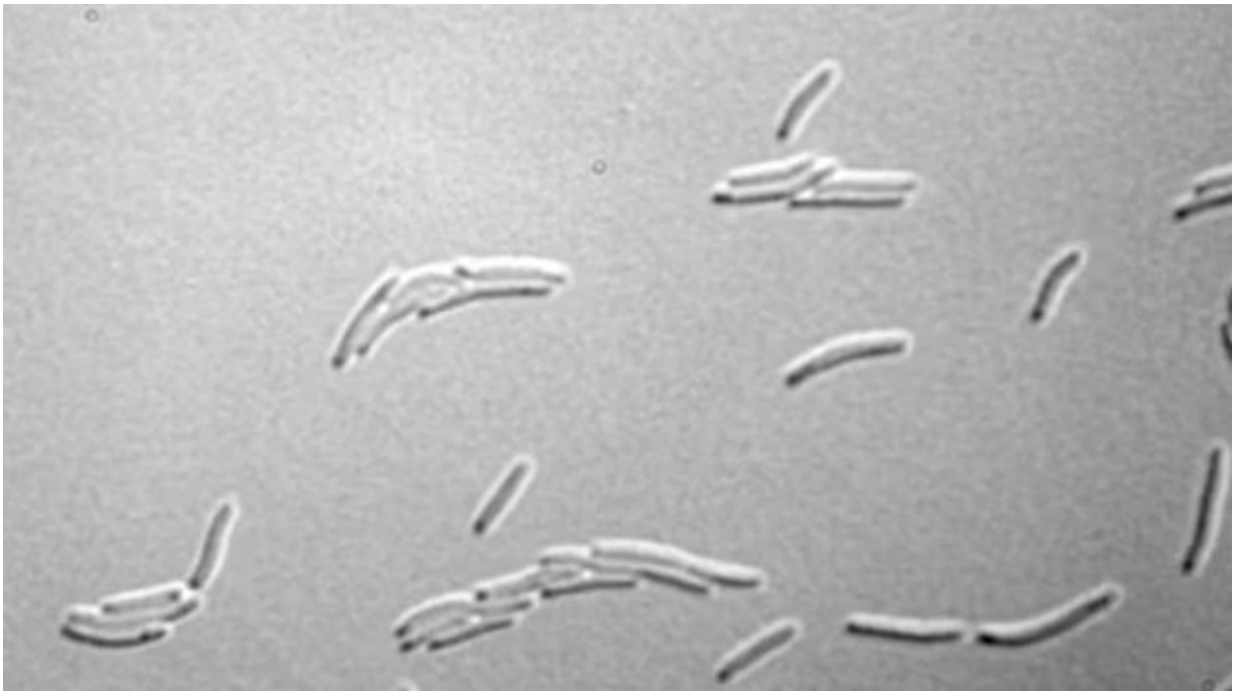

UC San Francisco scientists have developed an imaging tool that could soon allow doctors to locate and visualize bacterial infections in the body and to rule out other common causes of inflammation, such as autoimmune reactions.

On August 11, 2017 in *Scientific Reports*, the UCSF research team

reported that scans made with the imaging technique known as PET (positron emission tomography) effectively detected infections in mice caused by either of the two broad groups of bacteria, gram-negative and gram-positive, without generating a signal from other causes of inflammation.

The new work uses D-methionine, an amino acid that is readily absorbed by both gram-negative and gram-positive bacteria, to which a weakly radioactive atom has been chemically attached. If D-methionine-based PET imaging were approved for use in humans, it would let doctors facing challenging diagnoses find and treat infections much more quickly. The method could also give greater certainty to doctors when prescribing antibiotics, which, if overused, can promote resistant bacterial strains.

"We have these scenarios all the time," said Michael Ohliger, MD, PhD, an assistant professor of radiology and biomedical imaging at UCSF and one of the paper's senior authors. Patients will complain of chronic pain – around a new implant, or a recent surgical incision – and it is hard to tell whether the area is infected, or merely inflamed after the surgery, he explained.

"Currently, we tell if it's an infection or not based on other information and educated guesses. But this would allow us to stop guessing and know for sure," said Ohliger.

Collaboration Built a Better PET Imaging Agent

To perform PET imaging, doctors inject patients with small doses of "radiotracers" that bind to particular proteins or accumulate in tumors, inflamed areas, and other problem spots. The most commonly used tracer, a sugar-like molecule called FDG, accumulates in infected areas, but also follows immune cells to germ-free inflammation sites and

tumors. And the treatment for a sterile inflammation – usually some form of immunosuppressant – is the last thing doctors would want for a patient with an infection.

Other tracers, like radiolabeled antibodies that attach to particular bacteria, could easily miss many infectious strains, and can also emit a stronger signal from dead bacteria – which often have ruptured and spilled their contents – than from intact, live ones.

The search for a better radiotracer brought Ohliger together with fellow UCSF researchers David Wilson, MD, PhD, and Oren Rosenberg, MD, PhD, the paper's other senior authors. Rosenberg, an assistant professor of medicine, studies and treats infectious diseases, so he had long wished for a better imaging tool. Wilson, an associate professor of radiology, had a lab experienced in synthesizing and testing new imaging chemicals. "It's a great example of people from different fields combining their expertise," said Rosenberg.

The ideal molecule would detect only live bacteria, rather than bind to living or dead cells indiscriminately; it had play an active part in their growth. And it couldn't be a substance used by human cells, because then every cell in the body would "light up" on a PET scan.

Molecule Incorporated into Bacterial Cell Walls

One group of molecules that fit the bill was the D-amino acids, which bacteria take up from their environment to build their protective cell walls. These molecules are mirror images of the L-amino acids, which all organisms use to build proteins. But human cells make much smaller use of the D variety, so the team reasoned a radiolabeled D-amino acid would zero in on bacteria.

The team settled upon D-methionine, a minor component of the

bacterial cell walls that they found gives a strong signal when radiolabeled. To probe D-methionine's capabilities, the researchers injected infectious bacteria – both the gram-negative Staphylococcus aureus ("staph") and the gram-positive Escherichia coli – into mice. When they later injected D-methionine molecules tagged with a single radioactive Carbon-11 atom into the mice, PET scanning showed the radiotracer accumulating at both kinds of injection sites.

"Many radiotracers can detect gram-negative infections, but a lot of the infections we care about are gram-positive, so this is huge," said Wilson.

What's more, the imaging didn't detect the injections of dead bacteria, showing the diagnostic tool only picked up active infections.

Radiotracer Should be Quickly Adaptable

Unlike some other experimental radiotracers, "radiolabeled D-methionine is totally trivial to make," said Wilson. "There's automated equipment at many, many medical centers to make L-methionine," and making D-methionine simply requires starting with a slightly different molecule.

The team therefore hopes for rapid translation of their D-methionine findings for diagnosis in human patients. "I don't anticipate any difference between the mice and humans, since the tracer only targets bacteria," said Javier Villanueva-Meyer, MD, assistant professor of clinical radiology at the University of Virginia, who did the PET experiments as a postdoc in Wilson's lab.

If approved, the imaging could indirectly help in the fight against antibiotic resistance. "If a physician doesn't know whether they're dealing with an infectious or inflammatory issue, they may overprescribe broad-spectrum antibiotics, leading to antibiotic resistance," said Kiel

Neumann, PhD, an assistant professor of biomedical and radiology at the University of Virginia and the paper's other lead author. "With this approach, the clinician gets a definitive diagnosis."

Also, scanning during treatment to see if an infection is responding could help doctors avoid treating infections with antibiotics to which those infections are already resistant. "You would see immediately whether you're getting a response," said Rosenberg.

If the infection isn't responding, doctors would change treatment. And treatment could end quickly after the infection is defeated. "This is the epitome of precision medicine," said Neumann.

More information: Kiel D. Neumann et al. Imaging Active Infection in vivo Using D-Amino Acid Derived PET Radiotracers, *Scientific Reports* (2017). DOI: 10.1038/s41598-017-08415-x

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