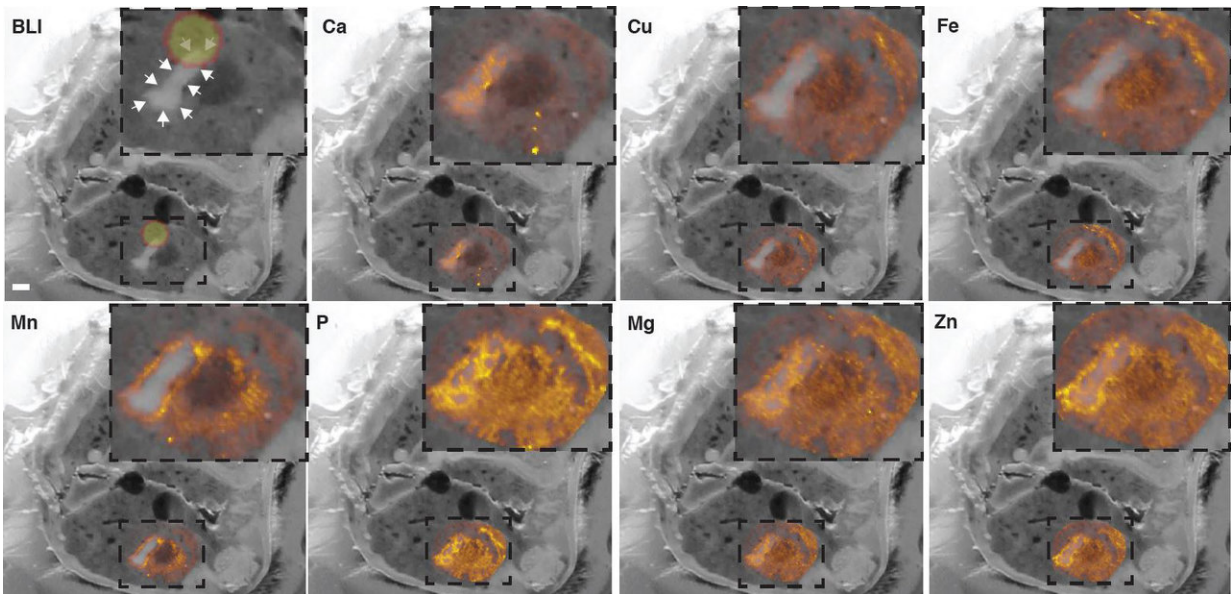


# New imaging approach offers unprecedented views of staph infection

March 14 2018



Visuals of kidney tissue sections from a mouse infected with *S. aureus*. This new imaging platform detects changes in the proteins and elements surrounding an abscess (indicated by white arrows). The resulting bioluminescent signal is depicted as a yellow sphere outlined in orange. The white bar represents a 1-mm scale. Credit: J.E. Cassat et al., *Science Translational Medicine* (2018)

Eric Skaar, PhD, MPH, marvels at the images on his computer screen—3-D molecular-level views of infection in a mouse. "I'm pretty convinced that these are the most advanced images in infection biology," said Skaar, Ernest W. Goodpasture Professor of Pathology.

Skaar and colleagues at Vanderbilt including James Cassat, MD, PhD, assistant professor of Pediatrics, combined multiple types of molecular imaging to probe an invasive *Staphylococcus aureus* ("staph") infection in the mouse. Their integrated imaging approach, reported this week in *Science Translational Medicine*, revealed new insights about staph infections and can be broadly applied to any health or disease state, Skaar said.

Antibiotic-resistant forms of staph are a leading cause of hospital-acquired infections, infectious heart disease, and pus-forming skin and soft-tissue infections.

The unique imaging resources available at Vanderbilt made the unprecedented 3-D imaging possible, Skaar said.

These resources include animal imaging technologies available through the Vanderbilt University Institute of Imaging Science, directed by John Gore, PhD, and imaging [mass spectrometry](#) technologies available through the Mass Spectrometry Research Center, directed by Richard Caprioli, PhD.

Skaar and his team are interested in the battle between host and pathogen for limited nutrients, particularly metals like iron, zinc and manganese. Identifying molecules involved in this struggle could point to novel diagnostic and therapeutic targets for infectious diseases. Over the past several years, the investigators have used various imaging modalities to study infection. Each approach has its own strengths, Skaar said. Magnetic resonance imaging (MRI), for example, shows how the physical anatomy changes in response to infection. Mass spectrometry reveals specific molecules with high sensitivity. Bioluminescence imaging (BLI) lets investigators study changes in gene expression in vivo.

"We came up with this idea of putting all of these imaging modalities together to ask really exciting questions," Skaar said. "When a mouse is infected with a horrible pathogen like staph, can we see how infection damages the tissue, how metals and metalloproteins (metal-binding proteins) are affected, and how bacteria change gene expression, all in one experiment?"

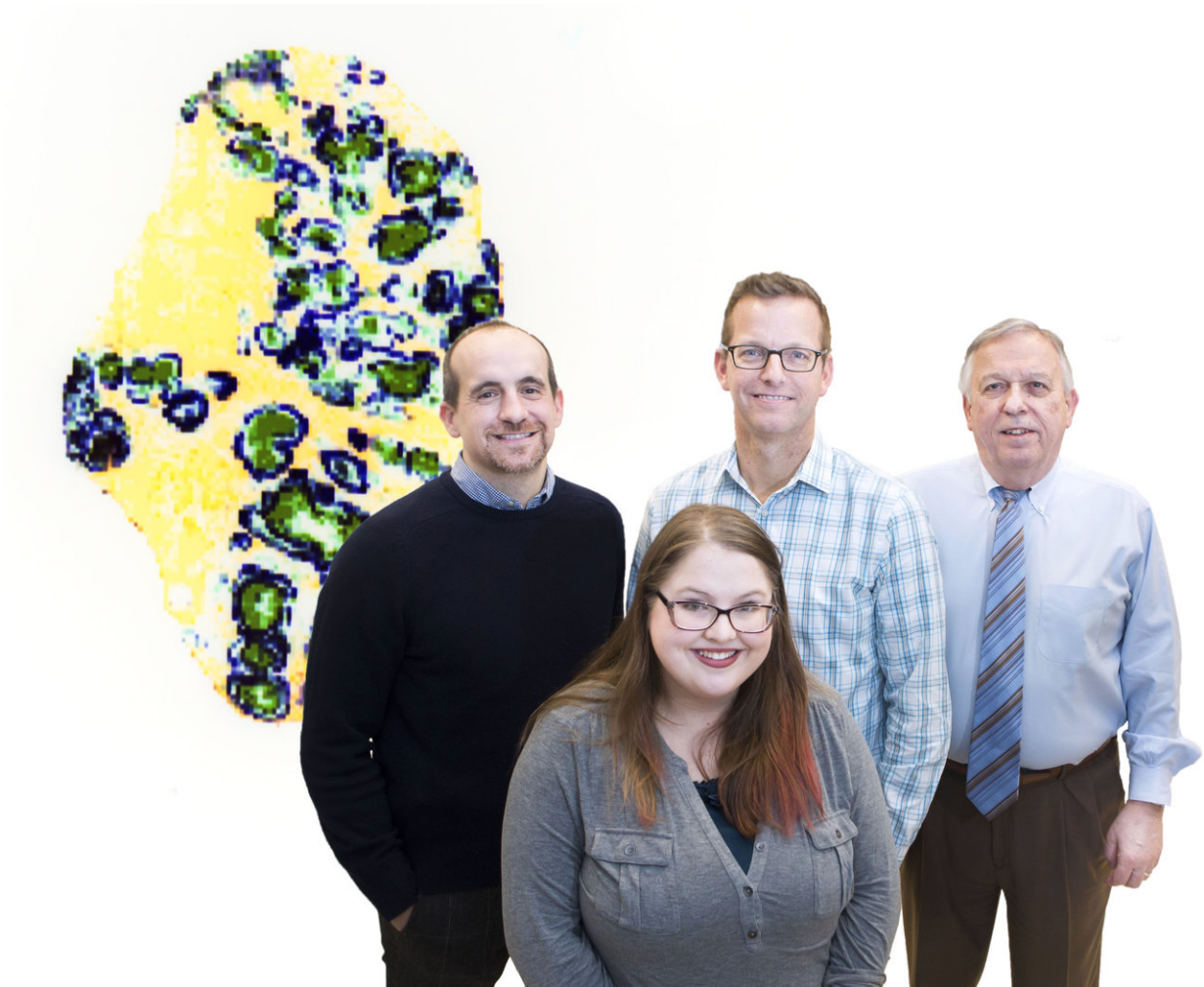
The approach was successful.

The investigators used MRI to visualize anatomy, imaging mass spectrometry to follow protein changes, another type of mass spectrometry to study the distribution of metals, and BLI to visualize bacterial genes that are expressed when iron is scarce.

Their studies showed that "not all abscesses are created equal," Skaar said. Historically, abscesses—the area of inflammation around a bacterial [infection](#)—have been considered to be identical and simply "big bags of pus." But Skaar and his team found that abscesses, even in the same tissue, have different molecular environments. Some metals are excluded from all abscesses, and some metals are in one abscess, but not in another. Within an abscess, the metal distribution is not uniform, suggesting an underlying [abscess](#) substructure, Skaar noted.

The staph bacteria responded to this molecular heterogeneity by expressing different genes in different abscesses—a discovery that is not possible to make using standard techniques that combine all abscesses together. The findings have implications for vaccine and therapeutic development.

"We can use these imaging modalities to identify proteins that are always expressed by the bacteria, as opposed to genes that are differentially expressed depending on the environment that the bacteria experience. Those factors would be excellent drug targets," Skaar said.



James Cassat, MD, PhD, left, Jessica Moore, PhD, Eric Skaar, PhD, and Richard Caprioli, PhD, are combining multiple imaging approaches to study the molecules involved in invasive staph infections. Behind the investigators is an imaging mass spectrometry image of mouse kidney infected with *Staphylococcus aureus*. Each color represents a unique protein species, and each protein has a unique spatial distribution within tissue. Credit: Vanderbilt University

The researchers also discovered that a key immune defense protein in neutrophils does not reach the bacterial cells. Looking at an image, Skaar

pointed out "the immune protein made by neutrophils is a blue cloud, coming to get the bacterial microcolony," represented by a purple dot.

The two colors never meet.

"There is a demilitarized zone in between the neutrophil protein and the bacterial microcolony," Skaar said, noting that the investigators do not know what is in this zone. "Whatever staph is doing, it's excellent at keeping the immune system from getting to it."

The multi-modality imaging approach is a powerful tool for making basic science discoveries about the host-pathogen interaction, which could reveal new therapeutic targets.

Using imaging to identify bacterial proteins might also be useful for diagnosing an infectious agent—and assessing its resistance to certain antibiotics—without having to culture it, Skaar said. Culture-free diagnosis would require a tissue sample that is amenable to imaging mass spectrometry.

**More information:** J.E. Cassat et al., "Integrated molecular imaging reveals tissue heterogeneity driving host-pathogen interactions," *Science Translational Medicine* (2018). [stm.sciencemag.org/lookup/doi/ ... scitranslmed.aan6361](https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.aan6361)

Provided by Vanderbilt University Medical Center

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