

Using nanobodies to block a tick-borne bacterial infection

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Host-seeking blacklegged tick. Credit: Centers for Disease Control and Prevention (CDC), CC0

Tiny molecules called nanobodies, which can be designed to mimic antibody structures and functions, may be the key to blocking a tick-borne bacterial infection that remains out of reach of almost all

antibiotics, new research suggests.

The infection is called human monocytic ehrlichiosis, and is one of the most prevalent and potentially life-threatening tick-borne diseases in the United States. The disease initially causes flu-like symptoms common to many illnesses, and in rare cases can be fatal if left untreated.

Most antibiotics can't build up in high enough concentrations to kill the infection-causing bacteria, *Ehrlichia chaffeensis*, because the microbes live in and multiply inside [human immune cells](#). Commonly known bacterial pathogens like *Streptococcus* and *E. coli* do their infectious damage outside of hosts' cells.

Ohio State University researchers created nanobodies intended to target a protein that makes *E. chaffeensis* bacteria particularly infectious. A series of experiments in [cell cultures](#) and mice showed that one specific nanobody they created in the lab could inhibit infection by blocking three ways the protein enables the bacteria to hijack immune cells.

"If multiple mechanisms are blocked, that's better than just stopping one function, and it gives us more confidence that these nanobodies will really work," said study lead author Yasuko Rikihisa, professor of veterinary biosciences at Ohio State.

The study provided support for the feasibility of nanobody-based ehrlichiosis treatment, but much more research is needed before a treatment would be available for humans. There is a certain urgency to coming up with an alternative to the antibiotic doxycycline, the only treatment available. The [broad-spectrum antibiotic](#) is unsafe for pregnant women and children, and it can cause severe side effects.

"With only a single antibiotic available as a treatment for this infection, if antibiotic resistance were to develop in these bacteria, there is no

treatment left. It's very scary," Rikihisa said.

The research is published this week in *Proceedings of the National Academy of Sciences*.

The bacteria that cause ehrlichiosis are part of a family called obligatory intracellular bacteria. *E. chaffeensis* not only requires internal access to a cell to live, but also blocks host cells' ability to program their own death with a function called apoptosis—which would kill the bacteria.

"Infected cells normally would commit suicide by apoptosis to kill the bacteria inside. But these bacteria block apoptosis and keep the cell alive so they can multiply hundreds of times very rapidly and then kill the host cell," Rikihisa said.

A longtime specialist in the Rickettsiales family of bacteria to which *E. chaffeensis* belongs, Rikihisa developed the precise culture conditions that enabled growing these bacteria in the lab in the 1980s, which led to her dozens of discoveries explaining how they work. Among those findings was identification of proteins that help *E. chaffeensis* block immune cells' programmed cell death.

The researchers synthesized one of those proteins, called Etf-1, to make a vaccine-style agent that they used to immunize a llama with the help of Jeffrey Lakritz, professor of veterinary preventive medicine at Ohio State. Camels, llamas and alpacas are known to produce single-chain antibodies that include a large antigen binding site on the tip.

The team snipped apart segments of that binding site to create a library of nanobodies with potential to function as antibodies that recognize and attach to the Etf-1 protein and stop *E. chaffeensis* infection.

"They function similarly to our own antibodies, but they're tiny, tiny

nano-antibodies," Rikihisa said. "Because they are small, they get into nooks and crannies and recognize antigens much more effectively.

"Big antibodies cannot fit inside a cell. And we don't need to rely on nanobodies to block extracellular bacteria because they are outside and accessible to ordinary antibodies binding to them."

After screening the candidates for their effectiveness, the researchers landed on a single nanobody that attached to Etf-1 in cell cultures and inhibited three of its functions. By making the nanobodies in the fluid inside E. coli cells, Rikihisa said her lab could produce them at an industrial scale if needed—packing millions of them into a small drop.

She collaborated with co-author Dehua Pei, professor of chemistry and biochemistry at Ohio State, to combine the [tiny molecules](#) with a cell-penetrating peptide that enabled the nanobodies to be safely delivered to mouse cells.

Mice with compromised immune systems were inoculated with a highly virulent strain of E. chaffeensis and given intracellular nanobody treatments one and two days after infection. Compared to mice that received control treatments, mice that received the most effective nanobody showed significantly lower levels of [bacteria](#) two weeks after infection.

With this study providing the proof of principle that nanobodies can inhibit E. chaffeensis infection by targeting a single protein, Rikihisa said there are multiple additional targets that could provide even more protection with nanobodies delivered alone or in combination. She also said the concept is broadly applicable to other intracellular diseases.

"Cancers and neurodegenerative diseases work in our [cells](#), so if we want to block an abnormal process or abnormal molecule, this approach may

work," she said.

More information: Wenqing Zhang et al, An intracellular nanobody targeting T4SS effector inhibits Ehrlichia infection, *Proceedings of the National Academy of Sciences* (2021). [DOI: 10.1073/pnas.2024102118](https://doi.org/10.1073/pnas.2024102118)

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