Redirecting the natural immune response to disrupt bacterial biofilms

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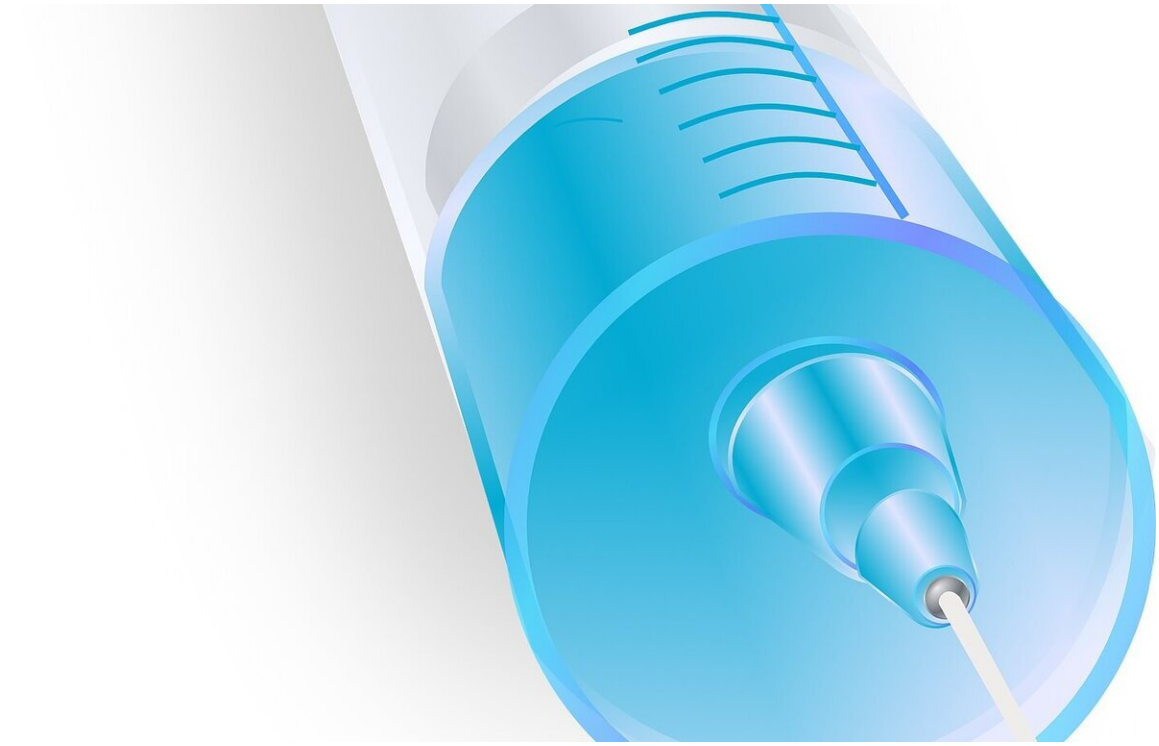

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Most bacterial species prefer to live in biofilms, where they are protected from antibiotic treatments and can lead to chronic and recurrent diseases in humans. To address this problem, researchers at Nationwide Children's Hospital have developed a novel synthetic peptide that mimics an essential component of bacterial biofilms. When used as

a vaccine, it redirects the natural adaptive immune response to disrupt bacterial biofilms so the immune system and/or traditional antibiotics can now effectively clear the infection.

"There is a tremendous need to develop therapeutic or preventative strategies to manage chronic and recurrent diseases, such as bladder and urinary tract infections, sinus infections, ear infections, infections of joints and wound infections," says Lauren Bakaletz, Ph.D., who is a principal investigator in and the director of the Center for Microbial Pathogenesis in the Abigail Wexner Research Institute at Nationwide Children's.

In a previous study, the team developed synthetic "tip-chimer" and "tail-chimer" peptides as a potential vaccine candidate and as a negative control, respectively. The two peptides mimic regions of an essential structural biofilm protein called integration host factor (IHF). IHF has a tail region that is exposed to the host immune system. Therefore, the investigators hypothesized the tail region might be preferentially recognized by the immune system, while the tip region that helps maintain biofilm stability may be hidden from the immune system within the interior of the biofilm.

The recent study, which was published in *NPJ Vaccines*, compared the abilities of antibodies directed at the tip-chimer peptide and purified IHF to disrupt a biofilm of nontypable Haemophilus influenzae in an experimental animal model of otitis media.

Four days after inoculation with H. influenza to the middle ears of the models, both ears were infused with the rabbit polyclonal antibodies to the tip-chimer peptide, antibodies to purified IHF or controls. Antibodies to the purified H. influenza IHF or to the tip-chimer peptide were both highly effective at eradicating the biofilm, and the middle ears of animals administered these treatments had either none or significantly

less biofilm remaining compared to animals given the controls.

Furthermore, for the two effective antibodies, disruption of the biofilm was maintained in the animals eight days later. Additional inspection showed that animals given the antibodies to the tip-chimer peptide had significantly less ear space occluded by biofilm than those given the antibody to the purified IHF.

"When we use antibodies to the tip-chimer peptide, not only are biofilms eradicated and bacteria killed by the immune system, but the middle ear goes back to looking like it never even had an infection in it. That's a pretty remarkable outcome," says Dr. Bakaletz, who is also a professor of Pediatrics and Otolaryngology at The Ohio State University College of Medicine.

Next, the team demonstrated in an in vitro assay of biofilm grown on a slide that the antibody to the tip-chimer peptide was significantly more disruptive than the antibody to the purified IHF.

After demonstrating with an antibody binding assay that the immune system, of the animal model and humans, does indeed have a preference for the tail region of IHF, the team then asked if the natural immune response can be redirected to recognize the tip region of the IHF protein using the tip-chimer peptide as a vaccine in the animal model. After active immunization of non-infected animals with the tip-chimer peptide, the team saw a significantly increased and exclusive preference for the tip-chimer peptide in the antibody binding assay than when the purified H. influenza IHF was used.

Having demonstrated preclinical feasibility of the tip-chimer vaccine, Dr. Bakaletz and her team are now taking steps to move toward human clinical trials.

"This approach, which can be used on any type of bacteria that form biofilms, is a platform technology that has a lot of potential. We hope this is going to be a way for clinicians to be able to use the antibiotics that have already been developed at a lower dose and thereby help limit the development of more antibiotic resistant bacteria," says Dr. Bakaletz. "If the vaccine is successful, we hope to be able to deliver a clinically positive outcome to patients who have resistant, chronic infections with limited results from repeated antibiotic therapy."

Provided by Nationwide Children's Hospital

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