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Biofilm battles: storming and repurposing the bacterial fortress

Bacterial communities build biofilms to protect themselves from external threats, such as antibiotics. But researchers are now taking aim at these bacterial shields.

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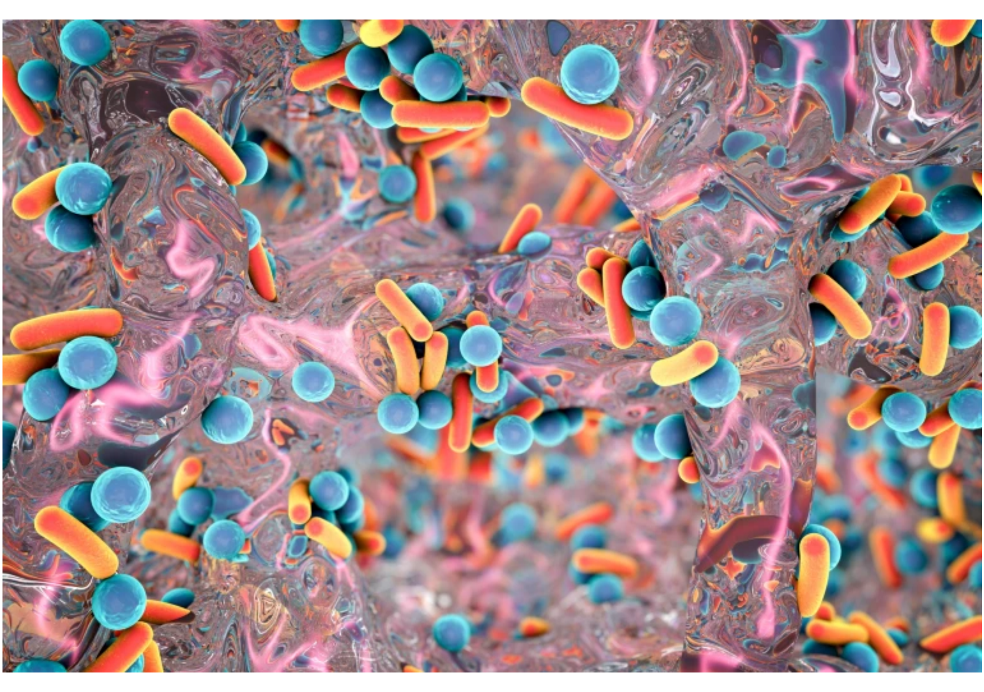


Most bacteria mimic multicellular life, forming a community connected by what's known as a biofilm. *Credit: Kateryna Kon/ Science Photo Library/ Getty Images.*

"Biofilms can be good, but when they go bad, then we have a real problem," says Lauren Bakaletz, director of the Center for Microbial Pathogenesis in the Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, Ohio. Bakaletz is among a growing list of scientists looking to treat some of the world's deadliest infections by manipulating the biofilms that enable them.

Bacteria are often thought of as free-swimming, single-celled organisms. While some bacteria do naturally exist in this individual 'planktonic' state, most bacteria mimic multicellular life, forming a community connected by a biofilm. These slime-like, three dimensional structures develop when bacteria secrete sugars, proteins, and other extracellular polymeric substances, including DNA, that coalesce into a dense meshwork that's capable of enveloping entire populations of bacteria — and protecting them.

"Most bacteria in nature prefer to live this way," explains Bakaletz. "Biofilms are sophisticated communal structures, with water channels, communication systems and even labour divisions. Unfortunately, they're also resistant to every treatment we have."

Amidst a pandemic of antimicrobial resistance, researchers like Bakaletz are looking for new ways to treat these increasingly persistent infections. Disrupting bad biofilms and cultivating good ones may be the edge they need.

A pandemic of biofilms

Antibiotic resistant bacterial infections cause roughly 2-5 million deaths worldwide annually[1]. Of these deaths, approximately 70% can be attributed to a collection of bacteria known as ESKAPEE pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp*., and *Escherichia coli*[1,2]. The propensity of ESKAPEE pathogens to develop multidrug resistance (and 'escape' treatment) has spurred the World Health Organization to designate these species as high priority targets for new drug development efforts.

"It's not trivial how horrible these infections are," explains Bakaletz. "When it prevents a child from undergoing chemotherapy, a lung transplantation, or when it occurs in the lungs of a person with cystic fibrosis, among many other situations, these infections can be life-shortening."

Part of their deadly effect stems from their ability to form biofilms.

The protective effect of biofilms on their inhabitants is still being studied, but it probably involves several factors. For one, their dense structure serves as a physical barrier, making it hard for antibiotics and immune cells to reach the bacteria inside. Even if a drug manages to penetrate the biofilm, it often encounters bacteria that are in a dormant state, where they've slowed down their growth and metabolism. Many antibiotics work best on active, growing cells. Additionally, within this community, bacteria can easily share drug resistance genes through a process called lateral gene transfer.

"Biofilms can be up to 1,000 times more resistant to antibiotics than free-swimming planktonic bacteria," explains John Hamilton, a physician scientist at Rush University, Chicago, Illinois, who studies biofilms and their role in periprosthetic joint infection (PJI). Most joint replacement surgeries are successful, but in approximately 1-2% of cases, patients develop PJI, an infection involving the joint prosthesis and adjacent tissue.

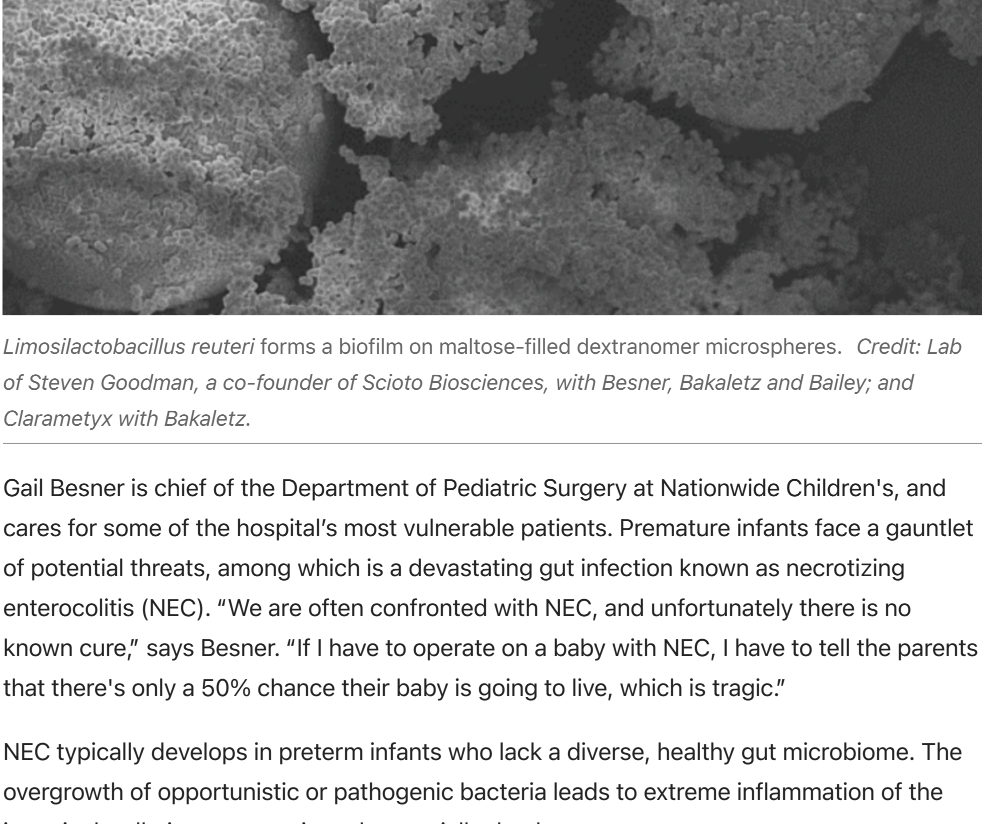
These infections are difficult to treat and can be devastating, leading to the death of approximately 20% of PJI patients[3]. Bacterial biofilm is a major factor contributing to the persistence of these infections. Hamilton hopes to improve PJI treatment success by preventing or disrupting biofilm formation, a task he undertakes with Bakaletz and her colleagues at Nationwide Children's Hospital.

"The Nationwide Children's team has done an incredible job inventing and characterizing an antibody that disrupts biofilm formation," adds Hamilton. The investigational antibody targets a protein known as DNABII that helps hold together biofilms. While the exact composition of biofilms may vary, they all use DNA from both bacteria and immune cells. Supercoiling of the DNA creates a durable material that acts like structural beams, holding the biofilm matrix together. As DNABII is a part of that structural beam, reducing its concentration may destabilize the biofilm. Bakaletz and her colleagues have shown that an antibody targeting DNABII can effectively dissolve biofilms and release the bacteria they contain[2,4,5].

"These newly released bacteria are about 8-20-fold more sensitive to antimicrobials and immune cells," explains Bakaletz. "We're hopeful that this will translate into an effective way to prevent PJI and other infections."

The team at Nationwide Children's, which includes Steven Goodman, principal investigator and co- discoverer of biofilm's DNABII-dependence, is focused on advancing this DNABII-targeting antibody through clinical trials. In parallel, researchers at the hospital are also exploring the therapeutic potential of creating, rather than destroying, biofilms.

Beneficial biofilms



Limosilactobacillus reuteri forms a biofilm on maltose-filled dextranomer microspheres. *Credit: Lab of Steven Goodman, a co-founder of Scioto Biosciences, with Besner, Bakaletz and Bailey; and Clarametyx with Bakaletz.*

Gail Besner is chief of the Department of Pediatric Surgery at Nationwide Children's, and cares for some of the hospital's most vulnerable patients. Premature infants face a gauntlet of potential threats, among which is a devastating gut infection known as necrotizing enterocolitis (NEC). "We are often confronted with NEC, and unfortunately there is no known cure," says Besner. "If I have to operate on a baby with NEC, I have to tell the parents that there's only a 50% chance their baby is going to live, which is tragic."

NEC typically develops in preterm infants who lack a diverse, healthy gut microbiome. The overgrowth of opportunistic or pathogenic bacteria leads to extreme inflammation of the intestinal wall, tissue necrosis and potentially death.

"If we could restore a more normal intestinal microbiome in these babies it would be immensely beneficial," explains Besner. Collaborating with Goodman and fellow principal investigator Michael Bailey, at Nationwide Children's, Besner examines a novel probiotic delivery system that aims to boost the level of *Limosilactobacillus reuteri* (Lr), a beneficial bacterium that's often reduced in NEC patients.

"All previous studies of probiotics have delivered the beneficial bacteria in their planktonic state, in which they are vulnerable to gastric acidity, competition with pathogenic bacteria, or the antibiotics that these patients are on," adds Besner. The results of these previous studies have been mixed. In contrast, her team has developed a method to deliver the probiotic *Lr* in its biofilm state. They believe that the same traits that make biofilms produced by pathogenic bacteria hard to treat can actually protect beneficial bacteria.

Preliminary results are promising. "We have data in newborn mice, rats and pigs showing that *Lr* in its biofilm state can protect the intestines from NEC, and can also protect the brain from the later effects of NEC," adds Besner.

"It's possible that we will see this probiotic in a clinical setting within the next five years," says Besner. The success of such a probiotic would be a welcome relief. "Our goal will be to never have to operate on these babies again."

Whether its building or destroying biofilms, success in this field is likely to have significant impact. "We need a transformative breakthrough," says Hamilton. "And something that translates across infection types is the presence of a biofilm."

For more information on the ongoing biofilm research at Nationwide Children's Hospital, visit their website

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