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Researchers Report Initial Success in Promising Approach to Prevent Tooth Decay

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Preventing cavities could one day involve the dental equivalent of a military surgical strike. A team of researchers supported by the National Institute of Dental and Craniofacial Research report they have created a new smart anti-microbial treatment that can be chemically programmed in the laboratory to seek out and kill a specific cavity-causing species of bacteria, leaving the good bacteria untouched.

The experimental treatment, reported online in the journal *Antimicrobial Agents and Chemotherapy*, is called a STAMP. The acronym stands for "specifically targeted antimicrobial peptides" and, like its postal namesake, STAMPs have a two-sided structure. The first is the short homing sequence of a pheromone, a signaling chemical that can be as unique as a fingerprint to a bacterium and assures the STAMP will find its target. The second is a small anti-microbial bomb that is chemically linked to the homing sequence and kills the bacterium upon delivery.

While scientists have succeeded in the past in targeting specific bacteria in the laboratory, this report is unique because of the STAMPs themselves. They generally consist of less than 25 amino acids, a relative pipsqueak compared to the bulky, bacteria-seeking antibodies that have fascinated scientists for years. Because of their streamlined design, STAMPs also can be efficiently and rapidly produced on automated solid-phase chemistry machines designed to synthesize small molecules under 100 amino acids, called peptides.

The first-generation STAMPs also proved extremely effective in the initial laboratory work. As reported in this month's paper, the scientists found they could eliminate the cavity-associated oral bacterium *Streptococcus mutans* within 30 seconds from an oral biofilm without any collateral damage to related but non pathogenic species attached nearby. Biofilms are complex, multi-layered microbial communities that routinely form on our teeth and organs throughout the body. According to one estimate, biofilms may be involved to varying degrees in up to 80 percent of human infections.

"We've already moved the *S. mutans* STAMP into human studies, where it can be applied as part of a paste or mouthrinse," said Dr. Wenyuan Shi, senior author on the paper and a scientist at the University of California at Los Angeles School of Dentistry. "We're also developing other dental STAMPs that target the specific oral microbes involved in periodontal disease and possibly even halitosis. Thereafter, we hope to pursue possible medical applications of this technology."

Shi said his group's work on a targeted dental therapy began about eight years ago with the recognition that everyday dental care had reached a crossroads. "The standard way to combat bacterial infections is through vaccination, antibiotics, and/or hygienic care," said Shi. "They represent three of the greatest

public-health discoveries of the 20th century, but each has its limitations in the mouth. Take vaccination. We can generate antibodies in the blood against *S. mutans*. But in the mouth, where *S. mutans* lives and our innate immunity is much weaker, generating a strong immune response has been challenging.”

According to Shi, a major limitation of antibiotics and standard dental hygiene is their lack of selectivity. “At least 700 bacterial species are now known to inhabit the mouth,” said Shi. “The good bacteria are mixed in with the bad ones, and our current treatments simply clear everything away. That can be a problem because we have data to show that the pathogens grow back first. They’re extremely competitive, and that’s what makes them pathogenic.”

To illustrate this point, Shi offered an analogy. “Think of a lawn infested with dandelions,” he said. “If you use a general herbicide and kill everything there, the dandelions will come back first. But if you use a dandelion-specific killer and let the grass fill in the lawn, the dandelions won’t come back.”

Hoping to solve the selectivity issue, Shi and his colleagues began attaching toxins to the homing region of antibodies. They borrowed the concept from immunotherapy, an area of cancer research in which toxin-toting antibodies are programmed to kill tumor cells and leave the nearby normal cells alone.

Despite some success in killing specific bacteria in the oral biofilm, Shi said his group soon encountered the same technical difficulty that cancer researchers initially ran into with immunotherapy. Their targeting antibodies were large and bulky, making them unstable, therapeutically inefficient, and expensive to produce. “That’s when we decided to get higher tech,” said Dr. Randal Eckert, a UCLA scientist and lead author on the study.

Or, as Eckert noted, that’s when they turned to the power of genomics, or the comparative study of DNA among species. Eckert and colleagues clicked onto an online database that contains the complete DNA sequence of *S. mutans*. They identified a 21-peptide pheromone called “competence stimulating peptide,” or CSP, that was specific to the bacterium. From there, they typed instructions into an automated solid-phase chemistry machine to synthesize at once the full-length CSP and a 16-peptide anti-microbial sequence, and out came their first batch of STAMPs.

After some trial and error, Eckert said he and his colleagues decided “to get even shorter.” They ultimately generated a STAMP with the same anti-microbial agent but with a signature eight-peptide CSP sequence to target *S. mutans*. “We pooled saliva from five people and created an oral biofilm in the laboratory that included a couple hundred species of bacteria,” said Eckert. “We applied the STAMP, and it took only about 30 seconds to eliminate the *S. mutans* in the mixture, while leaving the other bacteria in tact.”

As dentists sometimes wonder, what would happen if *S. mutans* is eliminated from the oral biofilm? Does another equally or more destructive species fill its void, creating a new set of oral problems? Shi said nature already provides a good answer. “About 10 to 15 percent of people don’t have *S. mutans* in their biofilms, and they do just fine without it,” he said. “Besides, *S. mutans* is not a dominant species in the biofilm. It only becomes a problem when we eat a lot of carbohydrates.”

Looking to the future, Shi said new STAMPs that seek out other potentially harmful bacterial species could be generated in a matter of days. He said all that is needed is the full DNA sequence of a microbe, a unique homing sequence from a pheromone, and an appropriate anti-microbial peptide. “We have a collection of anti-microbial peptides that we usually screen the bacterium through first in the laboratory,” said Shi. “We can employ the anti-microbial equivalent of either a 2,000-ton bomb or a 200-pound bomb. Our choice is usually somewhere in the middle. If the anti-microbial peptide is too strong, it will also kill the surrounding bacteria, so we have to be very careful.”

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