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The Fischetti lab exploits products derived from bacteria-killing viruses (or phages) to develop antibiotic alternatives for treating bacterial infections. This strategy identified bacteria-killing enzymes and a new immunotherapy to overcome antibiotic-resistant bacteria. One phage enzyme called lysin achieved successful outcomes in the second of three clinical trial phases, becoming the first antibiotic alternative to attain this goal.

Phages kill bacteria using enzymes called lysins, which dissolve the bacteria's cell wall. Fischetti's lab produces genetically engineered phage lysins that can kill major disease bacteria, such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Clostridium difficile*, *Bacillus anthracis*, and *Acinetobacter baumannii*. The enzymes are extremely potent; microgram quantities can destroy millions of organisms within seconds. They are also quite specific and, unlike antibiotics, only kill the disease-causing bacteria, without harming the beneficial bacteria. Importantly, resistance to lysins has yet to be seen.

Fischetti's studies have shown that when small amounts of phage lysins are given to infected mice, the disease-causing bacteria die rapidly. For example, Fischetti and his collaborators have shown that the phage enzyme Cpl-1 can cure mice with fatal pneumococcal pneumonia and completely reverse lung tissue damage when given 24 hours after infection. Similar results were seen in mice with life-threatening infections by antibiotic-resistant *S. aureus* by treating them with a lysin engineered specifically for staphylococci. A recent successful phase II clinical trial involved patients with methicillin-resistant *S. aureus*, or MRSA, a common infection that doesn't respond to conventional antibiotics. Results revealed that, among patients whose infection had spread to the blood, the positive response rate to treatment was 40 percent higher when a lysin-based drug called Exebacase was given together with antibiotics, compared to when antibiotics were administered alone. On follow-up, patients treated with lysin and antibiotics left the hospital sooner (6 vs 10 days) and had fewer relapses that resulted in re-admission to hospital (8% vs 15.4%) than patients treated with antibiotics alone. Like antibiotics, lysins may be developed to most disease-causing bacteria.

The lab also developed novel immunotherapies inspired by lysins. The Fischetti lab fused a portion of the *S. aureus*-specific lysins to immune molecules called antibodies, generating so-called "lysibodies" with the capacity to tag all staphylococci for destruction by human immune cells. Lysibodies may also be used to boost the immune response of Staphylococcus-infected patients. In mouse models, lysibodies were shown to protect the animals from infection by MRSA staphylococci. Since all attempts to develop vaccines to protect against staphylococcal infections have so far failed, lysibodies may be used passively in pre-surgical patients to protect them from hospital-associated *S. aureus* infections, particularly MRSA.

EDUCATION

B.S. in bacteriology, 1962
Wagner College

M.S. in microbiology, 1967
Long Island University

Ph.D. in microbiology, 1970
New York University

POSTDOC

The Rockefeller University, 1970–1972

Albert Einstein College of Medicine, 1972–1973

POSITIONS

Assistant Professor, 1973–1978

Associate Professor, 1978–1990

Professor, 1990–
The Rockefeller University

AWARDS

NIH Research Career Development Award, 1977

NIH MERIT Award, 1987, 1997

SELECTED PUBLICATIONS

Heselpoth, R.D. et al. PaP1, a broad-spectrum lysin-derived cationic peptide to treat polymicrobial skin infections. *Front Microbiol.* 13, 817228 (2022).

Raz, A. et al. Isolation of phage lysins that effectively kill *Pseudomonas aeruginosa* in mouse models of lung and skin infections. *Antimicrob. Agents Chemother.* 63, e00024–19 (2019).

Heselpoth, R.D. et al. Lysocins: bioengineered antimicrobials that deliver lysins across the outer membrane of gram-negative bacteria. *Antimicrob. Agents Chemother.* 63, e00342–19 (2019).

Raz, A. et al. Lysibodies are IgG Fc fusions with lysin binding domains targeting *Staphylococcus aureus* wall carbohydrates for effective phagocytosis. *Proc. Nat. Acad. Sci. U.S.A.* 114, 4781–4786 (2017).

Gilmer, D.B. et al. Novel bacteriophage lysin with broad lytic activity protects against mixed infection by *Streptococcus pyogenes* and methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 57, 2743–2750 (2013).