Antibiotic resistance is a problem plaguing both the scientific and medical communities. Through the process of evolution compounded with the overuse of antibiotics, bacteria have devised methods to protect themselves from the compounds that we use to prevent bacterial infection. These virulence factors that bacteria can acquire include capsules and biofilms that function as “protective coats,” chemical alterations to the antibiotic compounds themselves to make them ineffective, and the production of efflux pumps to eliminate the compound from the cell. The world is rapidly approaching an era where antibiotics will be ineffective to treat bacterial infections. However, new treatments are being discovered that can allow antibiotics to be effective, even in cases where the bacteria causing an infection is resistant to most antibiotics. During his talk at Pitt Science 2018 on October 19th, 2018, Dr. Paul Turner discussed how his laboratory is investigating a potential treatment option.

Dr. Turner is a professor of Ecology and Evolutionary Biology at Yale University. He received his bachelor’s degree in biological sciences at the University of Rochester, and he received his PhD in zoology at Michigan State University. After graduate school, he went on to be a postdoctoral fellow at the University of Maryland, a NSF-NATO fellow at the University of Valencia, and he completed a molecular virology fellowship through the NIH’s Laboratory of Clinical Investigation. Notably, he was named the Elihu Professor of Ecology and Evolutionary Biology at Yale University in 2017.

During his talk at Pitt Science 2018, Dr. Turner explained how his lab looks at evolutionary trade-offs. During evolution, compromises must be made by the organism. Evolutionary trade-offs occur when natural selection improves one trait at the expense of another. Dr. Turner mentioned an example where neck and back pain in humans stems from the fact that we walk upright. Primates who do not walk upright do not have this problem. Evolutionary trade-offs also occur in bacteria. For example, Dr. Turner mentioned how phage phi-6 infects the pilus of Pseudomonas syringae, a virulent plant bacterium. In order to evolve to prevent infection, P. syringae can lose the pilus. However, this adaptation reduces the conditional virulence of the bacteria as they then cannot move across leaves. Dr. Turner’s laboratory is interested in applying the concept of evolutionary trade-offs by looking for bacteriophages that target virulence factors in bacteria. Since virulence factors can provide antibiotic resistance to bacteria, there is a potential for a novel treatment method for patients infected with multidrug resistant (MDR) bacteria. To prevent cell death from bacteriophage infection, the bacteria would have to remove the virulence factor, making them sensitive to antibiotics.
An example that Dr. Turner extensively explained was that of OMKO1 infection of *Pseudomonas aeruginosa*. It is a species of bacteria that can be MDR. This is because they possess efflux pumps that can eliminate antibiotics from the cell, and the pumps are necessary for biofilm formation. In 2006, Dr. Turner’s lab discovered OMKO1. This bacteriophage binds to the outer membrane protein (OPrM) of MexAB and MexXY efflux pumps in *P. aeruginosa*. It was also found that OPrM is a highly conserved gene, making it a potentially good target for evolutionary trade-off phage therapy. In the lab, Dr. Turner and his colleagues discovered that *P. aeruginosa* is forced to stop the synthesis of efflux pumps to become resistant to the phage. This, in turn, makes the bacteria sensitive to antibiotics. This was shown in the lab in an experiment where the minimum inhibitory concentration (a measure of an antibiotic’s effectiveness) dropped dramatically in phage-resistant *P. aeruginosa*. It was also shown that phage-resistant cells could not make biofilms, and the bacteria became sensitive to a mixture of the antibiotics ceftazidime and ciprofloxacin. Next, it was found that the phage-antibiotic combination improved the survival of mice with an MDR lung infection. While the phage-antibiotic combination therapy was shown to work in mice, it remained to be seen if it would work in humans.

Recently, Dr. Turner’s laboratory had the opportunity to test the treatment on human volunteers. First, a treatment of OMKO1 with ceftazidime was successful in saving a patient infected with MDR *P. aeruginosa* on an aortic implant. He also talked about a 22-year old woman with cystic fibrosis and total drug resistant bacteria in sputum who was treated with a similar phage-antibiotic combination therapy. Her condition improved in 3 weeks. A 70 year old man with chronic obstructive pulmonary disease, small cell lung cancer, and a history of MDR *P. aeruginosa* was also successfully treated with a phage that targets the type IV pilus in the bacteria through a 10 day nebulizer treatment. The final case study presented by Dr. Turner looked at a 71 year old fire fighter with lung damage. He was infected with MRSA and MDR *P. aeruginosa*. A combination of phage OMKO1 and phage H6 with antibiotics improved his condition dramatically.

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The synergy between antibiotics and phages that target virulence factors can be successful in patients with MDR infections. Going forward, Dr. Turner is seeking investigational new drug status for his therapy method, and he is also looking to get broadly approved for clinical trials that target MDR \textit{P. aeruginosa}. He hopes that his lab’s treatment method can be used in emergency compassionate-care therapy as well as in the prophylactic prevention of MDR infection in individuals who undergo medical procedures with an elevated risk of MDR infection (such as with cardiografts that are susceptible to biofilm growth). His lab is also looking for other bacterial targets for phage-based evolutionary trade-offs. Even while phage therapy continues to be a topic of debate in both the medical field and the public, Dr. Turner and his colleagues show that there is hope for patients infected with antibiotic-resistant bacteria through a novel phage therapy method.

References:

