PROFILE

Profile of Paul E. Turner

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"There is a lot of power in addressing general questions in biology using the smallest inhabitants of the planet," says Paul E. Turner, the Rachel Carson Professor of Ecology and Evolutionary Biology at Yale University. Conducting interdisciplinary and experimental evolution studies of microbes, Turner and his colleagues elucidate virus evolution and ecology and host–parasite interactions, among other subjects. Turner, who was elected to the National Academy of Sciences in 2019, also conducts applied research on the development of virus-based therapies that hold promise for combating antibiotic-resistant bacterial pathogens. His Inaugural Article (1) contributes to that body of research, which is helping to launch a new era in phage biotechnology.

Earliest Memories Concern Biology

When Turner reflects on his childhood, spent in the San Francisco Bay Area and central New York, fond memories concerning biology come to his mind: Exploring forests, visiting zoos, reading books by Stephen Jay Gould, and watching television programs like *Wild Kingdom*. Alice Kendrick, a teacher at Jamesville-DeWitt High School in New York, cultivated his interest in biology. "She is awesome and made a lasting positive impact," Turner says.

His parents were both college-educated and employed in professions related to theology and education. Turner says, "Although they were not scientists, my parents appreciated that I was captivated with biology and they provided supportive encouragement for me to pursue a career in this discipline."

Navigating a Field with Low Diversity

After earning a bachelor of arts degree in biological sciences from the University of Rochester in 1988, Turner began graduate studies at the University of California, Irvine. There he met evolutionary biologist Joseph Graves, Jr, then a postdoctoral fellow. Turner says, "This prominent African American scientist served as my early life coach, helping me to navigate a field where diversity remains very low."

Turner transferred to Michigan State University, where he earned a doctorate in zoology in 1995. His doctoral advisor was evolutionary biologist Richard

Paul E. Turner. Image credit: Michael Marsland (Yale University, New Haven, CT).

Lenski. "Rich taught me how to be a scientist and to always push the envelope by pursuing research on 'big ideas,'" he says. Turner's communication skills were honed by advisor Lin Chao during his years as a National Science Foundation minority postdoctoral fellow at the University of Maryland Department of Biology. He then completed a second postdoctoral stint at the University of Valencia, Spain, where advisor Santiago Elena taught him how to conduct interdisciplinary research bridging virus evolution and systems biology. The experience abroad was followed by an Intramural Research Training Award postdoctoral fellowship at the National Institutes of Health Laboratory of Clinical Investigation in 2000.

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Microbes as Model Systems

Turner's research frequently uses microbes as model systems to test evolutionary and ecological theories. With Lenski and a colleague, Turner used plasmids as models to test the theorized systematic trade-off between infectious and intergenerational modes of parasite transmission (2). The researchers confirmed that infectious parasites cannot evolve to simultaneously maximize horizontal and vertical transfers between hosts. Contrary to the trade-off hypothesis, however, they found that host density had little effect on the evolution of one mode of transfer versus the other.

With Chao, Turner used RNA viruses to test the prisoner's dilemma strategy of game theory, which holds that defection (selfishness) evolves despite the greater fitness pay-off that would result if all players were to cooperate. He says, "In this case, we used virus interactions within cells to show that selfish behavior can evolve despite lowering overall population fitness, consistent with predictions from economic game theory models" (3). Viral cooperation and defection were respectively defined as the manufacturing and sequestering of shared intracellular products.

Specialism Versus Generalism

Turner's RNA virus studies have examined the evolutionary genetics of specialism versus generalism with the aim of determining how and why viruses evolve to become broad or narrow in their host breadth. In 2000, with Elena, he showed how single-host use in RNA viruses leads to evolved specialization, whereas growth on alternating hosts selects for virus generalists (4). Turner and his team then demonstrated that viruses can rapidly speciate when evolving on a new host species (5).

Another analysis of RNA viruses found that when genetic changes randomly occur in their genomes, populations can evolve mutational robustness that buffers deleterious fitness effects (6). Since robust viruses tolerate higher mutation frequencies, evolution of robustness could permit less accurate genome replication.

Peer Recognition

Turner received numerous professional offers before accepting a position at Yale as assistant professor in the university's Department of Ecology and Evolutionary Biology in 2001. In 2002 he was invited to join the US delegation in a joint United States–Russia workshop on infectious disease in Novosibirsk. "I was honored to be selected for the delegation and to visit the State Research Center of Virology and Biotechnology (Vector), which houses one of only two samples in the world of the smallpox virus," Turner says.

At Yale, Turner was named an associate professor with tenure in 2006 and full professor and departmental chair in 2011 before receiving his present title. Since 2002, Turner has also served as a faculty member in the medical school's microbiology graduate program, and since 2011, he has served as a visiting faculty fellow at The Marine Biological Laboratory in Woods Hole, Massachusetts.

Turner regularly serves as an invited participant in conferences, with one of the most important in his field being the Gordon Research Conference on Microbial Population Biology. After attending for several years, Turner was elected by his peers to chair the 2013 conference.

Contributions to Viral Ecology

Turner's active teaching schedule has not deterred his research program. An ongoing area of study concerns viral ecology, which addresses how viruses interact molecularly within their hosts, between their hosts, and with their environment. In particular, Turner and his laboratory members have used both phages and viruses of eukaryotes as laboratory models for elucidating evolutionary rules of RNA virus emergence.

For example, Turner and his colleagues showed how within-host growth and between-host transmission determine whether RNA viruses go extinct or successfully emerge in a new host species (7). In another study his team demonstrated that a history of prior RNA virus evolution in multiple hosts can foster the emergence of these viruses in novel hosts (8).

Evolutionary Constraints of Viruses

Turner is adept at identifying genetic trade-offs that occur when organisms evolve adaptive traits for one purpose while suffering reduced performance in an unselected trait. He says, "Uncovering evolutionary constraints of RNA viruses is useful in designing therapies that target these weaknesses in virus fitness across environments." Exemplifying this effort, Turner's team combined studies of RNA virus evolution and structural biology to show that a single mutation can explain how viruses obey the classic survival versus reproduction trade-off observed widely in macroorganisms (9).

Additionally, Turner's team has demonstrated that viruses suffer evolutionary trade-offs across selective temperatures and across differing innate immune profiles of hosts. Turner and colleagues, for example, used RNA viruses to show that biological populations may be incapable of evolving to adapt in environments with random temperature changes, which is consistent with the predictions of some climate change models (10). His team also tracked molecular evolution in RNA virus populations to reveal that different mutations occur when viruses jump rapidly versus gradually to novel host species (11).

Earth's Most Successful Inhabitants

Turner makes a compelling case that viruses are more biologically successful than cellular life, such as in a 2013 review that he coauthored (12). The article examines gauges of biological success, including numerical abundance, environmental tolerance, type biodiversity, reproductive potential, and widespread impact on other organisms.

The authors conclude that although viruses are often challenged by abiotic fluctuations in temperature and moisture, along with challenges due to other factors related to their dynamic environments like host

immune function, they often readily adapt and seem to enjoy an advantage for evolvability. Turner says, "There is abundant evidence that viruses are the most successful inhabitants of Earth."

Novel Phage Therapy Approach

Turner's applied research includes looking for natural products that may be useful in combating important pathogens. In 2016, he and his team isolated from a Connecticut pond a lytic phage, OMKO1, which attacks the common multidrug-resistant pathogen *Pseudomonas aeruginosa* (13). OMKO1 attaches to the bacteria's cell membrane at the site of an efflux pump mechanism that evolved to rid the cell of antibiotics. Experimental evolution identified a trade-off where evolution of resistance to phage attack leads to changes in the bacterial membrane that make the pump mechanism less efficient. As a result, *P. aeruginosa* is rendered sensitive to several classes of antibiotics.

Two years after the discovery, OMKO1 was applied to a patient's aortic graft that had become infected with *P. aeruginosa* (14). The antibiotic ceftazidime was also administered. Following a single application, the phage/antibiotic treatment resolved the infection with no signs of recurrence. Turner says, "This was a rare example of a successful phage therapy in a US patient where a virus was used to combat a chronic multidrug-resistant bacterial infection." In 2018, Turner's laboratory and the start-up company Felix Biotechnology entered into an agreement with Adaptive Phage Therapeutics to examine therapeutic phages in clinical trials.

Since the published case study (14), 12 more patients have been successfully treated using comparable approaches. For these and other achievements, Turner was elected to fellowship in the American Academy of Arts & Sciences and the American Academy of Microbiology in 2019.

New Era in Phage Biotechnology

Turner's research has led to renewed interest in the medical potential of phages. In a recent review, he and colleagues compared phage therapy with chemical antibiotics and highlighted their potential synergies when used in combination (15). The article emphasizes that the new approach not only uses viruses to kill pathogenic bacteria, but also selects for increased antibiotic sensitivity in the remaining bacterial population.

Turner's Inaugural Article (1) reports the discovery of phage U136B that infects *Escherichia coli* by relying on an efflux protein system of the bacteria in addition to a structural barrier molecule. The study shows that evolution of phage resistance could occur through loss or modification of these structures, which cause the bacteria to become sensitive to antibiotics. The researchers, however, also discovered a subset of bacterial mutations that avoided the trade-off due to pleiotropy. Turner therefore remains cautiously optimistic about the future of phage therapeutics. As he says, "Phage technology needs more basic science and research on why it works and why it can fail."

Several of the article's (1) coauthors are Turner's undergraduate students. He also often collaborates with his graduate students and postdoctoral fellows, crediting his students and mentees for their inspiration and help over the years. Turner is additionally grateful for the support of his wife Mary Beth Decker, an ecologist and evolutionary biologist at Yale, as well as their two daughters.

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