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Hijacking a *Pseudomonas aeruginosa* Weapon of Self-Destruction as a Potential Therapeutic Tool

Pseudomonas aeruginosa, a bacterial pathogen notorious for its role in hospital-acquired infections, frequently displays antibiotic resistance, making infections difficult to treat. This resistance warrants the development of novel ways to combat serious infections. *P. aeruginosa* cells can deploy nano-sized, spring-loaded spears known as pyocins to kill competing *P. aeruginosa* strains in a ruthless competition against its own kind. Not all *P. aeruginosa* cells in a given population produce pyocins; typically, they are a last-resort effort to be useful by bacteria that have suffered DNA damage and will soon die. In the current regulatory model, pyocin production is repressed by a protein called PrtR, which becomes cleaved when DNA is damaged, allowing an activator protein PrtN to initiate pyocin production. Our lab discovered that deleting a gene called *xerC* causes cells to overproduce pyocins. As expected, supplying these cells with an uncleavable version of PrtR blocks the production of functional pyocins, but, surprisingly, does not inhibit all expression of the pyocin genes. Conversely, inducing production of the activator protein PrtN in the uncleavable PrtR strain fails to restore functional pyocins, suggesting that pyocin regulation involves more factors than just PrtR and PrtN. We hypothesize that two long overlooked but highly conserved genes in the pyocin gene cluster, which have conspicuously low expression in the uncleavable PrtR mutant, are important factors in pyocin production.

I am expressing these two genes under inducible control in the uncleavable PrtR mutant by themselves and with *prtN* to see if I can restore functional pyocin production. Promisingly, expression of just the two genes restored moderate pyocin production, and I am working on co-expressing *prtN* to restore high pyocin production.

Understanding the molecular mechanisms behind the pyocin pathway will help us leverage the potential of pyocins as a therapeutic tool against *P. aeruginosa* infections. Lethal to many strains of *P. aeruginosa*, pyocins pose as an excellent therapeutic candidate, as they will not contribute to antibiotic resistance and will exclusively target *P. aeruginosa* cells, leaving intact the beneficial bacteria in our bodies.