Evolution is a fundamental challenge in medicine. It is the root cause of the continued rise of antimicrobial-resistant pathogens, the emergence of new infectious diseases, and the progression of chronic infections and cancers. Evolution is also an indispensable tool used in biotechnology for creating proteins and cells with radically new functions not found in nature and for optimizing complex biological systems. Yet, here too, evolution can be problematic, as an obstacle to stably and predictably engineering cells for biomanufacturing and therapeutic applications. My research group studies genome dynamics in microbial systems in which we can watch evolution in action. One of our main goals is learning how to better predict and control genome dynamics to make genetic engineering and synthetic biology safer and more effective. In this seminar, I will first describe the population genetic and molecular mechanisms behind the rise and eventual fall of hypermutator bacteria in the Lenski long-term evolution experiment with *Escherichia coli*. Then, I will present an integrated strategy for reinforcing synthetic biology against unwanted evolution that incorporates a computational tool for the negative design of DNA sequences, genome-scale engineering to reduce mutagenesis–with an example using the naturally transformable bacterium *Acinetobacter baylyi* ADP1, and a directed evolution procedure for isolating antimutator cells that have lower-than-natural mutation rates. Finally, I will briefly describe how we have been able to apply a broad-host-range genetic toolkit to engineer bacteria native to the gut microbiome of honey bees to affect their behavior and improve their health.