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Investigating viral attenuation by promoter knockout: a systems approach

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Abstract: Live attenuated viral vaccines provide the most robust and longest lasting immune response. Yet designing them *a priori* to have reduced growth capacity and also to be robust to evolutionary reversion can be challenging. On the one hand, genome editing methods now enable us to create almost any conceivable viral genome composition. Yet understanding and predicting how engineered genomes will behave and evolve is a challenge. Here we adopt a systems approach in studying a simple attenuation design in bacteriophage T7: promoter knockout. Either or both promoters for the two most highly expressed genes were abolished. Overall fitnesses, major phenotypes and gene expression levels were measured for all initial genomes and for genomes evolved toward for fitness recovery. Initial genomes behaved broadly as expected, but the genomes showed an unexpected ability to evolve back to high fitness. Genome sequences, RNA Seq and proteomics reveal the molecular foundations of the attenuations and recoveries. Overall, the work suggests that a systems approach is ultimately yielding to understanding, if not predicting the consequences of genome editing and evolutionary recoveries of simple genomes.

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