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Using deep mutational scanning to identify the determinants of antibiotic resistance

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USING DEEP MUTATIONAL SCANNING TO IDENTIFY THE DETERMINANTS OF ANTIBIOTIC RESISTANCE

Current drug discovery platforms have proven incapable of supplying enough new antibiotic types to meet the challenge of rapidly developing clinical resistances. New techniques that specifically incorporate potential resistance adaptations during design are necessary. In cases of known specific resistance mechanisms, a biophysical approach may allow rational development of existing drugs that escape resistance. In this work, we use deep mutational scanning (DMS), a next-generation sequencing-based technique that reports on the site-specific fitness effects of mutations across an entire protein, to investigate the contribution of Virginiamycin acetyltransferase (VatD) to several streptogramin analogues. While generating this, we have developed a simplified workflow for generating programmable DMS libraries incorporating insertions and deletions, providing a novel measure of a sequence-function relationship. Based on our dataset we propose strategies to increase the longevity and efficacy of antibiotics.