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Designing ß-Lactamase Inhibitors to Restore the Efficacy of Existing Antibiotics

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Designing β-lactamase Inhibitors to Restore the Efficacy of Existing Antibiotics

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We use a combination of computer simulations and biochemical experiments to discover druggable pockets in proteins that are not present in their crystallographic structures, which we call cryptic sites. TEM-1 β-lactamase is an enzyme that degrades common β-lactam drugs, rendering bacteria resistant to common antibiotics such as penicillin. By developing β-lactamase inhibitors that bind cryptic sites, we will restore the efficacy of many existing antibiotics. A high-throughput screen was developed and used to discover an inhibitor and two activators, and we are currently trying to verify that these compounds bind in their predicted cryptic pockets by mutating key binding residues identified by computational docking experiments. Through the mutation of these residues, we have been able to alter the effects of one of the compounds on the enzyme, giving strong evidence that the compound binds in the predicted site. We are currently collecting more data on the binding of the other two compounds, and there is evidence both of these compounds bind in their predicted cryptic sites. We are also working on obtaining structural data in the form of NMR and crystallography to compare against our docking and experimental results.