Structure-based discovery and optimization of inhibitors for the class D β-lactamase OXA-24/40

β-lactams are the most widely prescribed class of antibiotics in clinical use today. In response to their extensive use and misuse, resistance developed and is now one of the most pressing public health crises of the 21st century. β-lactamases are the most widespread resistance mechanism to β-lactam antibiotics, rendering the antibiotic inactive through hydrolysis of the defining β-lactam ring. The class D β-lactamases are of particular concern since they are observed to hydrolyze carbapenems, the most potent β-lactams in clinical use, and are not typically inhibited by β-lactam-based inhibitors. In part, resistance derives from the structural similarity of the inhibitors to the β-lactams antibiotics. Therefore, an urgent need exists for novel inhibitors that do not resemble β-lactam substrates. The molecular docking program DOCK was used to screen of the fragment and lead-like subsets of the ZINC database for non-covalent inhibitors of the carbapenem-hydrolyzing class D β-lactamase OXA-24/40. Inhibitors from each subset were shown to inhibit the activity of OXA-24/40 with K_i values ranging from ~100 μM to 1 mM. Structures of OXA-24/40 in complexes with several of these novel inhibitors were determined to resolutions from 1.67 to 1.80 Å. Analogs of each of the leads were tested, and several showed modest improvements in binding affinity for the enzyme. These DOCK-predicted non-covalent inhibitors offer an opportunity to advance these compounds toward becoming viable class D β-lactamase inhibitors.

Rachel Powers
Joshua Mitchell
Brian Basinski
Uyen Pham