Bacterial antibiotic resistance has become a real treatment problem in medicine. It is mostly due to the activity of β-lactamases – enzymes produced by Gram-negative pathogens, responsible for cleavage of β-lactam rings in penicillins, cephalosporins and carbapenems, inactivating these drugs. In clinical use there are only a few inhibitors of β-lactamases, however, antibiotic resistance is still developing due to their clinical overuse [1]. Therefore further investigation of the reaction mechanisms of β-lactamases followed by rational inhibitor design becomes a very challenging medical need.

Carbapenems are the most potent β-lactam antibiotics and key drugs for treating infections by Gram-negative bacteria. As proven experimentally, carbapenems effectively escape activity of most beta-lactamases due to slow deacylation of the acyl-enzyme intermediate. However, the SFC-1 enzyme from Serratia fonticola hydrolyzes antibiotics, and so there is no effective treatment against those bacteria. In this study, we present crystal structures of the class A carbapenemase SFC-1 from Serratia fonticola complexed with the carbapenem meropenem as its Ser70 Ala (Michaelis) and Glu166 Ala (acylenzyme) mutants [2].

Molecular dynamics simulations indicated the mode of binding that occurs in both the Michaelis and acylenzyme complexes of wild-type SFC-1 (Figure A). In carbapenem-inhibited class A β-lactamases, it is proposed that the deacylating water molecule is deactivated by interaction with the carbapenem 6α-IR-hydroxyethyl substituent. Structural comparisons with such enzymes suggest that in SFC-1 subtle repositioning of key residues (Ser70, Ser130, Asn132 and Asn170) enlarges the active site, permitting rotation of the carbapenem 6α-IR-hydroxyethyl group and abolishing this contact (Figure B). Further comparison of the deacylation reaction mechanisms by quantum mechanics/molecular mechanics approach reflected the significant difference in activation energy barriers for different β-lactamases.