INSIGHT INTO IMPACT OF HIGH RESISTANCE-CAUSING MUTATIONS ON PENICILLIN BINDING PROTEIN 3 OF *H. INFLUENZAE* SUGGESTS AN ALTERNATIVE APPROACH FOR COMBATING ANTIBIOTIC RESISTANCE

Almotasem belah ALHAMWI[1], Canan ATILGAN[2], and Ozge SENSOY[1,3]

[1] Graduate School of Engineering and Natural Sciences, Istanbul Medipol University
[2] Faculty of Engineering and Natural Sciences, Sabanci University
[3] Regenerative and Restorative Medicine Research Center (REMER), Research Institute for Health Sciences and Technologies (SABITA), Istanbul Medipol University, 34810 Istanbul, Turkey
phone: +905394479729, fax: + (216) 681 5621, email: almotasem.alhamwi@std.medipol.edu.tr

ABSTRACT

Currently prescribed antibiotics target predominantly the catalytic site of bacterial proteins. Moreover, they focus on wild-type proteins; however, bacteria adopt mutations to survive in their challenging environment. According to World Health Organization report (2022), resistant bacterial infections cause annually 4.95 million deaths. Therefore, there is an urgent need for identifiying alternative allosteric regions to combat with this life-threatening problem. Towards this end, we set out to investigate impact of high-resistance causing triple mutation (S385T + L389F + N526K) on dynamics of a prioritized resistant pathogen, *H. influenzae*, by computational techniques. We focused on FtsW-penicillin-binding protein 3 (PBP3) complex, which was shown to display resistance towards β-lactam antibiotics that prevent bacterial cell wall synthesis. We identified a reaction coordinate, an angle on the N-terminal periplasmic modulus (N-t) of PBP3 that displayed differences between the wild type and mutant protein. Interestingly, it adopted smaller values in the latter, which were associated with higher number of residues participating in the allosteric communication network on the pathway that connects the N-terminal module to the catalytic site. Moreover, the angle also impacted orientation of the transpeptidase domain with respect to the cytoplasmic membrane and the exposure of the catalytic site. In the wild type, the catalytic site was more exposed which presumably enabled accession of the site by antibiotics. We also picked up representative conformations of the wild-type and the mutant protein where we performed covalent-docking on the catalytic site using β-lactam antibiotics such as cefixime, ceftaroline, and amoxicillin. The mutant PBP3 displayed higher binding affinity than the wild type suggesting that it might hydrolyze the antibiotic more effectively. All these data suggest that the newly identified region can be targeted to modulate the activity of the resistant PBP3. Therefore, this study provides a new perspective for developing effective molecules to combat with resistant bacteria.

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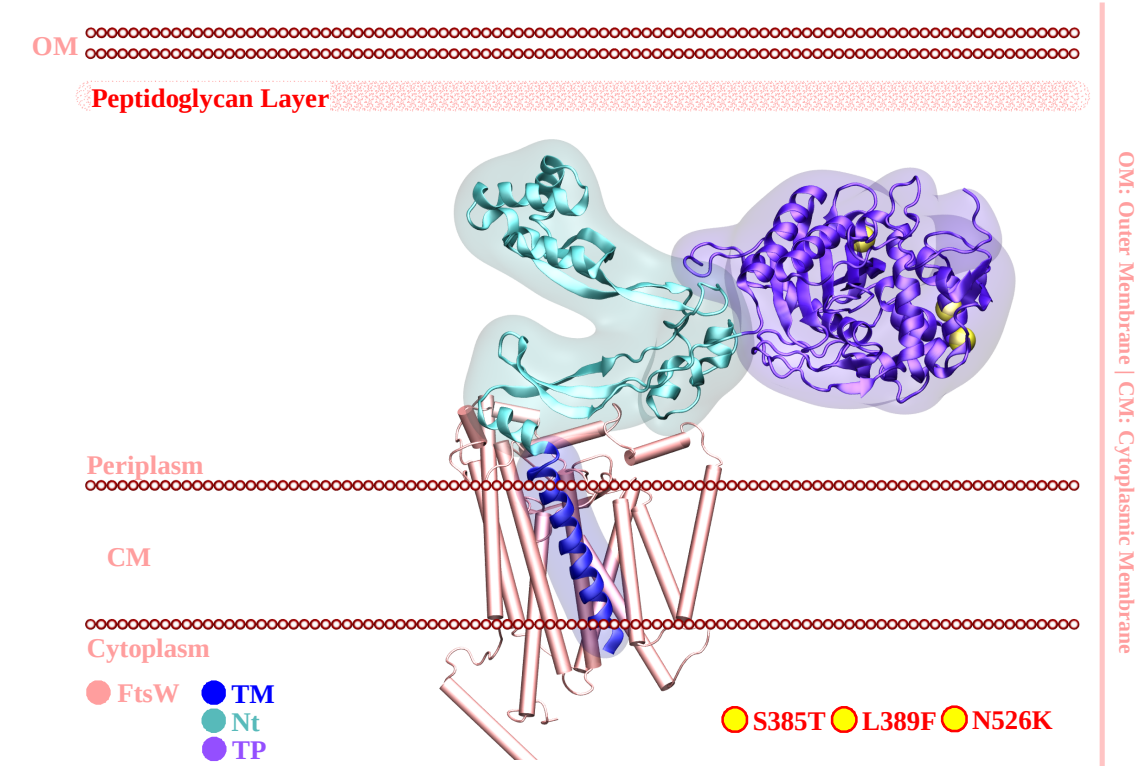
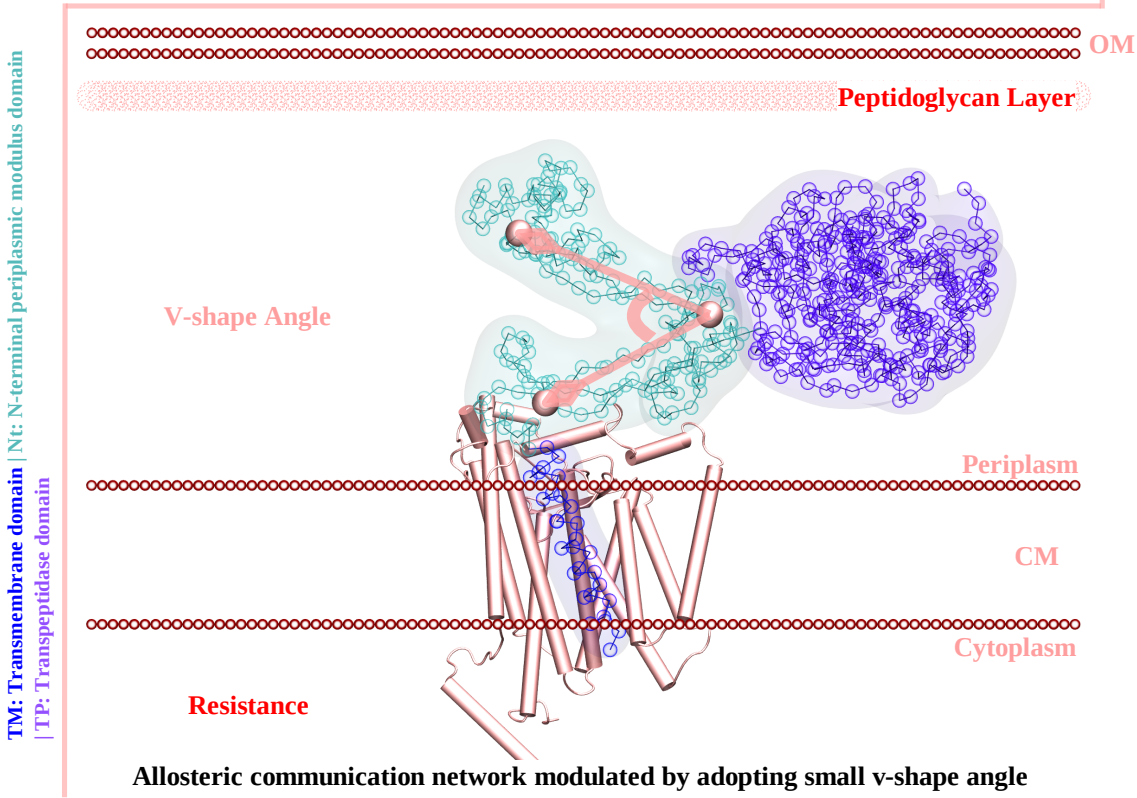


3D structure of FtsW-PBP3 Complex



Allosteric communication network modulated by adopting small v-shape angle