

## Elucidating the Mechanism of Antibiotic Resistance in *Enterobacteriaceae* by Metallo- $\beta$ -Lactamases: A Genomic and Proteomic Study to Design New Drug Molecules

Members of *Enterobacteriaceae* from clinical and non-clinical settings have become one of the most important cause of hospital and community acquired infections<sup>1</sup>. As these are becoming increasingly resistant to conventional antibiotics.

The dissemination of metallo- $\beta$ -lactamases genes ( $bla_{\text{MBLs}}$ ) in *Enterobacteriaceae*, by conjugation, imparts resistance to other species against penicillins, cephalosporins and carbapenems. The widespread of  $bla_{\text{MBLs}}$  pose a greater risk of infection as these genes are located on plasmids and flanked by IS elements/integrans/transposons and can disseminate across species<sup>2</sup>. Moreover, these plasmids carry genes for co-resistance to other antibiotics such as aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicols, etc<sup>3</sup>.

New Delhi Metallo- $\beta$ -lactamase (NDM) is one such MBL that has a very broad substrate profile, including carbapenems, but sparing monobactams<sup>4</sup>. The rapid and global dissemination of NDM producing Gram-negative species possess major public health threat<sup>5,6,7</sup>.

In India, the presence of NDM-1 in community acquired infections suggests that  $bla_{\text{NDM-1}}$  is widespread in environment and posing a greater risk to the community health<sup>8</sup>. This scenario is of immense concern because no new antibiotic is in the pharmaceutical pipeline that is effective against NDM-1 producers. Thus, there is pressing need for the development of new drug molecules against MBLs.

In the light of above background, we wanted;

- To learn more about the prevalence of NDM-producing *Enterobacteriaceae* in the environment of India
- To study the genetic environment around  $bla_{\text{NDM}}$  to locate IS elements/integrans/transposons/resistant islands mutations/new genes that aid antibiotic resistance in *Enterobacteriaceae*.
- To understand the molecular basis of antibiotic hydrolysis by NDM and to design novel inhibitors against it.

### Work done to date:

For this study, we collected environmental sample (sewage water) from Aligarh, India. PCR and sequence analysis showed that the bacterial strains were having 2 NDM variants (NDM-4 and NDM-7). These bacterial strains showed very high minimum inhibitory concentrations against following antibiotics Imipenem, Meropenem, Aztreonam, Ceftazidime, Cefotaxime, and Cefoxitin, Gentamicin, Ticarcillin/Clavulanic acid. Conjugation experiment confirmed that  $bla_{\text{NDM}}$  gene is present on plasmid and its dissemination can easily occur. Moreover, replicon typing and PCR based genetic environment study were also performed.

### Significance

The study will open new vista to understand the role of genetic markers around  $bla_{\text{MBLs}}$  in multidrug resistance. Moreover, potential new lead drug molecules can be identified against MBLs may be further optimized for clinical use.

### References

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