SMART Teams 2013-2014
Research and Design Phase

Milwaukee Academy of Science SMART Team

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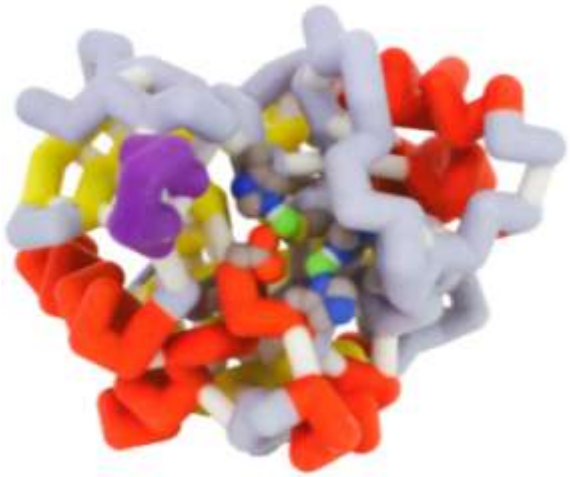
The Emergence of a Superbug: NDM-1 and its Role in Carbapenem Resistance

PDB: 3Q6X

Primary Citation: Zhang, H., Hao, Q. (2011). Crystal structure of NDM-1 reveals a common ß-lactam hydrolysis mechanism. *FASEB Journal.* 25:2574-2582.

Format: Alpha carbon backbone



RP: Zcorp with plaster

Description:
Imagine going to the doctor to be treated for a normally treatable infection only to find that no effective treatments exist because all conventional antibiotics are ineffective. In some regions of the world, antibiotic prescription isn't regulated and overuse has lead to antibiotic resistance. Carbapenems are a class of antibiotics that inhibit bacterial cell wall synthesis and are often used as a last resort treatment for bacterial infections. New Delhi metallo-ß-lactamase-1 (NDM-1) is an enzyme that occurs in several types of bacteria and conveys resistance against carbapenems. The Milwaukee Academy of Science SMART Team (Students Modeling A Research Topic) modeled the NDM-1 protein using 3D modeling technology. NDM-1 is a single-chain polypeptide consisting of 270 amino acids found in the bacterial periplasmic space. The NDM-1 active site consists of two loops (L10 and the highly flexible L3) and two zinc ions. These zinc ions are held in place by three histidine amino acids (H120, H122, H189) on L3 and a triplet of amino acids on L10. The zinc ions bind to and sever the ß-lactam ring on carbapenems, inhibiting its antibiotic properties. It's the flexibility of L3 that gives NDM-1 the ability to hydrolyze the full spectrum of carbapenems. Researchers are concerned because the gene for NDM-1 is located on a plasmid that's frequently passed via horizontal gene transfer among various species of bacteria. An understanding of NDM-1's structure and function may prevent an outbreak of bacteria equipped with the NDM-1 enzyme.

Specific Model Information:

- The alpha carbon backbone is colored is steel gray.
- Beta sheets are highlighted in yellow.
- Alpha helices are highlighted in red.
- Zinc ions, displayed in ball and stick and colored lime green, bind to and sever the ß-lactam ring on carbapenems, which acts as an inhibitor to antibiotic and carbapenem properties.
- The loop 3 of the alpha carbon backbone is highlighted in purple as its flexibility enables it to fit a wide variety of carbapenems, thus disabling them to properly do their job.
- Amino acids (H120, H122, H189< H250, D124 and C208), displayed in ball and stick and colored in cpk, are part of the active site.
- The heme group is displayed in ball and stick and colored in cpk.
- Carbon monoxide is displayed in ball and stick and colored in cpk.
- Amino acids (Leu29, Phe43, Phe46, His 64, Val68 and His93) responsible for stabilizing the ligand are displayed in ball and stick and colored in cpk.
- Amino acids (Gly, Leu and Gln), displayed in ball and stick and colored in cpk, are swappable with His64.
- Structural supports and hydrogen bonds are colored white.

http://cbm.msoe.edu/smartTeams/

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