

Discovery of new agents against “superbugs” with novel mechanism of action

The uncontrolled use of β -lactam antibiotics has selected several strain of bacteria with different mechanism of resistance. In particular, some Gram – such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp.* known with acronym **ESKAPE**, are almost completely resistance to several treatments. The different mechanism of resistance are: increased the drug efflux capacity, reduced permeability of the bacteria wall, selection of mutants in the transpeptidase (target enzyme of the β -lactam antibiotics) and more importantly the increase expression of the β -lactamase responsible for the inactivation of β -lactam. Regarding the β -lactamase, they are now express with very large spectrum of activity (ESBL). The modern carbapenem active against Gram+ e Gram- are now the first line therapy against these pathogens, unfortunately the increase of their use is leading to the new mechanism of resistance generating the so call “superbugs” that are not affected by these agents.

There are two β -lactamase known, one the most studied is the Serin β -lactamase in fact there are drugs approved, the second are the metal β -lactamase (MBL) and there not drugs approved. In particular, for the MBL, the B1 subclass is the most relevant in the clinical isolates and the isoform NDM-1, isolated in 2008, is the most dangerous because of its diffusion in several bacterial strain all over the word. The discovery of potent selective inhibitor of NDM-1 in combination with β -lactam antibiotics is currently the frontier of antibiotic research. The present project is focalized on the identification of new molecular classes, with unprecedented mechanism of action for the inhibitions of the resistance mechanism identified with the computational techniques called PPI-FIT, the molecule will be synthesized with the modern rapid analogs technique, fully characterized and tested in specific assays to determine the efficacy against “superbugs”.

Tutor

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