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An extremely narrow range antibiotic with a new mode of action against *Neisseria gonorrhoeae*.

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Background

Antibiotic resistance is reaching worrisome levels in *Neisseria gonorrhoeae* (Ng). It is thus of the utmost importance to find new avenues to try to curb this incoming health threat. Ng is becoming resistant to a wide range of antibiotics including the current recommended treatment. One way towards the prevention of this issue would be to find antibiotics with novel modes of action potentially orthogonal to modes of action of commonly used antibiotics.

Aim/Methods

The vast majority of our antibiotic arsenal is stemming from the evolutionary arms race between microbes. We focused our attention onto a bacterial strain discovered in the lab that presented a growth inhibition to Ng strains grown on solid media. Crude extractions from cell suspension also maintained a strong inhibition highly specific to Ng. We decided to identify and isolate the compound(s) responsible and decipher the mode of action.

Results

Chromatography of crude extracts led to reproducible active fractions. We used a combination of mass spectrometry, genomics, bacterial genetics and NMR to identify the compound with the highest activity. We used both chemical and transposon mutagenesis to screen for mutants resistant to this compound. The yield of revertants was extremely low. All revertants targeted the same protein. This protein is a very common membrane protein poorly studied. We investigated the role of this protein in Ng and found that it is involved in its overall physiology affecting in part membrane integrity, membrane potential, type IV pili retraction forces and ion homeostasis. Besides, revertants to our compound tend to be more sensitive to a variety of other antibiotics.

Conclusions

We have identified and characterized a compound with an exquisite narrow-range specificity to Ng. The Neisserial protein giving rise to resistance plays an important role in bacteria's metabolism. Given that the role of this membrane protein is very poorly characterized and that the revertants are more sensitive to a wide range of other antibiotics, there is hope that this compound could be used in conjunction with other antibiotics to hamper the rise of antibiotics resistance in Ng.