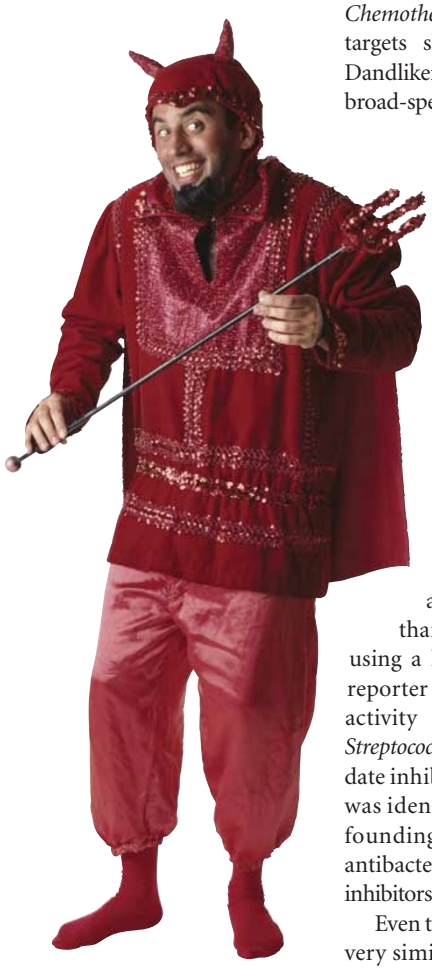
ANTI-INFECTIVES

Better the devil you know

To continue to effectively treat respiratory diseases caused by bacteria — which kill more than 50 million people each year — a continuous supply of potent antibacterials is a prerequisite to combat emerging antibacterial resistance. However, the last new class of antibacterials to reach the clinic was the oxazolidonones, which were identified in 1980. One way to tackle the problem of developing new antibacterials is to identify new bacterial targets and design new compunds to inhibit them, but this isn't the only solution. Research just published in *Antimicrobial Agents and Chemotherapy* shows that traditional targets should not be neglected. Dandliker *et al.* have identified a new broad-spectrum antibacterial class by screening for inhibitors of the bacterial ribosome.



The ribosome can be inhibited by several antibacterials in common use, including chloramphenicol, tetracycline and oxazolidonones, and because each antibacterial binds to a different site on the ribosome, resistance to one antibacterial agent does not produce resistance to all the antibacterials that target the ribosome. Dandliker *et al.* screened an existing library of more than 300,000 small molecules using a high-throughput cell-free reporter system for translation activity purified directly from *Streptococcus pneumoniae*. One candidate inhibitory molecule, A-73210, was identified and designated as a founding member of a new class of antibacterials called novel ribosome inhibitors or NRIs.

Even though NRIs are chemically very similar to quinolones, such as ciprofloxacin, which inhibit DNA gyrase activity, their mode of action is different because NRIs specifically block translation. NRIs have broad-spectrum antibacterial action, which restricts bacterial growth. Indeed, NRIs are active against Gram-positive and Gram-negative bacteria, including *S. pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Haemophilus influenzae* — all important respiratory pathogens. NRIs are even active against multiply antibacterial-resistant clinical *S. pneumoniae* and *S. aureus* isolates — indicating that NRIs inhibit translation by a new mechanism. Finally, resistance to NRIs arose by point mutations in the 16S rRNA and the S3 ribosomal protein at a low frequency of 1×10^{-8} in *S. pneumoniae*, and significantly, mutants resistant to the new class of compounds were not cross-resistant to any other antibacterial that targets bacterial translation. This indicates that NRIs bind to a distinct ribosomal site compared with antibacterials presently in use.

This exciting news shows that even established libraries and targets can yield new inhibitors if the screening strategy is well-designed, which provides hope for the battle with antibacterial resistance.

Susan Jones

References

ORIGINAL RESEARCH PAPER Dandliker, P. J *et al*. Novel antibiotic class. *Antimicrob. Agents Chemother.* **47**, 3831–3839 (2003)
FURTHER READING Walsh, C. Where will new antibiotics come from? *Nature Rev. Microbiol.* **1**, 65–70 (2003)