

## HIGHLIGHT ADVISORS

### ADRIANO AGUZZI

UNIVERSITY HOSPITAL OF  
ZÜRICH, ZÜRICH, SWITZERLAND

### NORMA ANDREWS

YALE UNIVERSITY SCHOOL OF  
MEDICINE, NEW HAVEN, CT, USA

### ARTURO CASADEVALL

THE ALBERT EINSTEIN COLLEGE  
OF MEDICINE, BRONX, NY, USA

### RITA COLWELL

UNIVERSITY OF MARYLAND  
BIOTECHNOLOGY INSTITUTE,  
BALTIMORE, MD, USA

### STANLEY FALKOW

STANFORD UNIVERSITY  
SCHOOL OF MEDICINE,  
STANFORD, CA, USA

### TIMOTHY FOSTER

TRINITY COLLEGE, DUBLIN,  
IRELAND

### KEITH GULL

UNIVERSITY OF OXFORD,  
OXFORD, UK

### NEIL GOW

UNIVERSITY OF ABERDEEN,  
ABERDEEN, UK

### HANS-DIETER KLENK

PHILIPPS UNIVERSITY,  
MARBURG, GERMANY

### BERNARD MOSS

NIAID, NATIONAL INSTITUTES OF  
HEALTH, BETHESDA, MD, USA

### JOHN REX

ASTRAZENECA, CHESHIRE, UK

### DAVID ROOS

UNIVERSITY OF PENNSYLVANIA,  
PHILADELPHIA, PA, USA

### PHILIPPE SANSONETTI

INSTITUT PASTEUR,  
PARIS, FRANCE

### CHIHIRO SASAKAWA

UNIVERSITY OF TOKYO,  
TOKYO, JAPAN

### ROBIN WEISS

UNIVERSITY COLLEGE LONDON,  
LONDON, UK

## 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 oxazolidinones, which were identified in 1980. One way to tackle the problem of developing new antibacterials is to identify new bacterial targets and design new compounds 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 oxazolidinones, 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  $1 \times 10^{-8}$  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)