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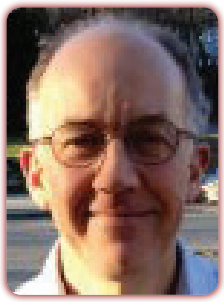

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## Negamycin induces translational stalling and miscoding by binding to the small subunit head domain of the *Escherichia coli* ribosome

Negamycin is a natural product with broad-spectrum antibacterial activity and efficacy in animal models of infection. The antibiotic inhibits cellular protein synthesis and causes cell death, but its precise mechanism of action remained to be determined. Here, we show that single point mutations within 16S rRNA of *Escherichia coli* that confer resistance to negamycin are in close proximity of the tetracycline binding site within helix 34 of the small subunit head domain. As expected from its direct interaction with this region of the ribosome, negamycin was shown to displace tetracycline. However, in contrast to tetracycline-class antibiotics which serve to prevent cognate tRNA from entering the translating ribosome, single-molecule fluorescence resonance energy transfer investigations revealed that negamycin specifically stabilizes near-cognate ternary complexes within the A site during the normally transient initial selection process to promote miscoding. The crystal structure of the 70S *E. coli* ribosome in complex with negamycin, determined at 3.1 Å resolution, shed light on this finding by showing that negamycin occupies a site that partially overlaps with that of tetracycline. Collectively, these data suggest that the small subunit head domain contributes to the decoding mechanism and that small-molecule binding to this domain can either prevent or promote tRNA entry by altering the initial selection mechanism after codon recognition and prior to GTPase activation.

### Biography

Ed T. Buurman received his PhD degree in Chemistry from the University of Amsterdam, followed by postdoctoral research at the University of Chicago (IL) and University of Aberdeen (U.K.). He then joined the collaborative antifungal drug discovery effort of Scriptgen Pharmaceuticals with Hoechst Marion Roussel, currently part of Sanofi. Three years later he moved to AstraZeneca R&D Boston where he has since worked in various capacities on many aspects of antimicrobial drug discovery, ranging from target validation to lead optimization and support of NDA filings. Most of this work has been published to benefit the wider antibacterial drug discovery community.

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