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Structural Basis of Apramycin Recognition of the Ribosomal Decoding Site. Qing Han, Qiang Zhao, Sarah Fish, Klaus B. Simonsen, Dionisios Vourloumis, Jamie Froelich, Dan Wall, Thomas Hermann*, Anadys Pharmaceuticals, Inc. 3115 Merryfield Row, San Diego, CA 92121; *Dept. of Chemistry and Biochemistry, UCSD, La Jolla, CA 92093.

Aminoglycoside antibiotics bind to 16S rRNA near the mRNA decoding site and induce miscoding during translation. Apramycin is unique among aminoglycosides in achieving antibacterial specificity by substitution of the 2-DOS ring at the 4-position only. In contrast to other aminoglycosides, the main effect of apramycin is inhibition of elongation by blocking translocation. To decipher the molecular recognition of the rRNA target by apramycin, we determined the crystal structure of apramycin bound to an oligonucleotide containing the bacterial decoding site.

The crystal structure reveals a unique mode of apramycin interaction with the decoding-site RNA. Apramycin binds to the decoding-site internal loop in the major groove and extending into the minor groove. A pseudo-base pair interaction of the apramycin bicyclic sugar with A1408 and alignment of the terminal sugar with C1409-G1491 in a pseudo-base triple are key interactions. Docking of the complex structure to the 30S subunit indicates that apramycin binding might involve ribosomal protein S12, which is a key trigger element for ribosome translocation.