Antibiotics targeting the 50S ribosomal subunit

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Ribosomes are universal biological machines responsible for the translation of the genetic code into the composition of functional proteins. The ribosome therefore plays a central role in the life cycle of any living organism. The inhibition of ribosomal protein synthesis through interference with the key functions of the ribosome – decoding and peptide bond formation - is consequently a major target of large variety of different classes of antibiotics [1].

Among the clinically relevant antibiotics affecting the ribosome, the macrolides and their semi-synthetic derivatives, which were known to bind the large or 50S ribosomal subunit, are of particular interest. Most of the compounds belonging to this class of antibiotics, do not inhibit peptide bond formation, but inhibit the elongation of the poly-peptide chain produced by the ribosome. In the presence of the macrolides, ribosomes are still capable of peptide bond formation, but protein synthesis stalls after a few elongation cycles. The mechanism of inhibition of protein synthesis by the macrolides has recently been determined by crystallographic studies of the 50S subunit from *Deinococcus radiodurans* in complex with different antibiotics [2]. These studies clearly confirmed, that macrolides block the entrance to the ribosomal exit tunnel, which guides the linear poly-peptide chain from the peptidyl transferase centre (PTC) to the chaperone binding site at the bottom of the 50S subunit, roughly 100Å away from the PTC. The tunnel hence protects the nascent chain against premature digestion by proteases. Though it was originally believed, that the tunnel just provides a passive path for the nascent chain, the investigation of a rather unusual macrolide, troleandomycin, showed that elements within the tunnel are able to discriminate and regulate synthesis in a sequence specific manner [3].

The activity of macrolides against pathogens is severely compromised by antimicrobial resistance, a problem common to most antibiotics used in therapeutic treatment of infectious diseases. The study of antimicrobial resistances and new antibiotics bound to the ribosome provides therefore valuable information for the development of new or better drugs.

Recent crystallographic studies of the 50S subunit in complex with azithromycin and ABT-773, a so called ketolide, showed on a molecular basis, how these new macrolides derivatives could partially overcome antimicrobial resistances [4]. The ketolides ABT-773 and telithromycin [5] utilize interactions with the ribosome, which differ substantially from those of the classical macrolides like erythromycin. The enhanced binding to regions which are less affected by modifications leads finally to a much better susceptibility and antimicrobial activity. Azithromycin is a very recently approved anti-infective drug with superior pharmacological characteristics. But it’s also unique among the macrolides, since it binds cooperatively in two positions within the ribosomal tunnel, which leads to a stronger binding and higher efficiency, two rather desired pharmacological properties.

To further enhance the resolution of the crystal structures of the ribosomal subunits, a prerequisite for structure based drug design, several experiments have been performed at BW6/HASYLAB with the aim to improve the experimental conditions leading to superior diffraction properties.

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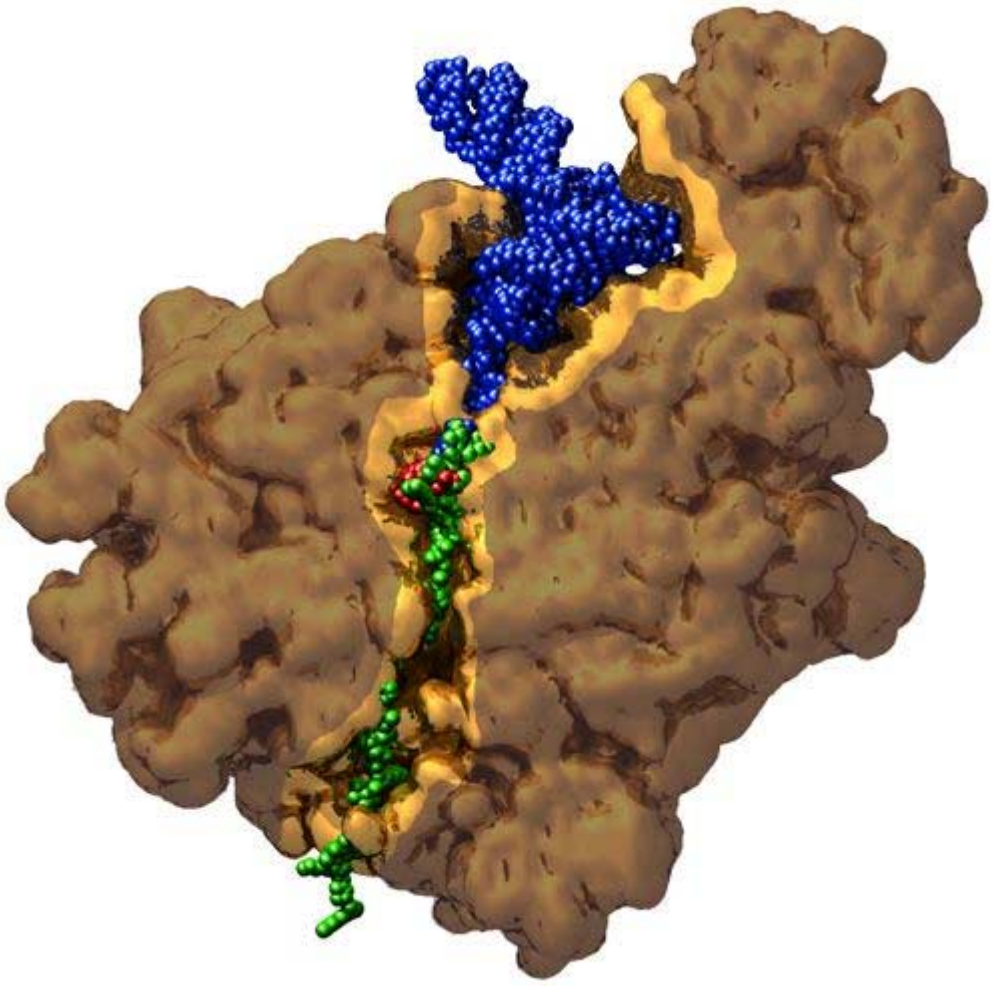

Figure 1: A cut through the 50S ribosomal subunit from *Deinococcus radiodurans*, illustrating the activity of macrolides antbiotics. The exit tunnel is highlighted in gold, and filled with a model for the poly-petide chain, which is attached to a tRNA molecule (in blue). The macrolides blocking the tunnel are shown in red.

References

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