Chasing after Antibiotic Leads

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DOI 10.1016/j.chembiol.2009.10.001

The emergence of drug-resistant pathogens has prompted the search for new antibacterials. In this issue of *Chemistry & Biology*, Starosta et al. identify specific thiopeptide-antibiotic precursor lead compounds using three complementary high-throughput translation machinery assays.

The ribosome is a major target for antibiotic action. Many natural antibiotics inhibit cell growth by binding to the ribosome and inhibiting protein synthesis (Sutcliffe, 2005). They have served as the quintessential drugs used to combat bacterial infections. However, the spread of resistant strains has become a real threat (Walsh, 2009), creating a need for strategies that allow the rapid identification and evaluation of fresh antibiotic leads. This is not an easy task, since a variety of different interaction modes between the antibiotic and the ribosome are possible (e.g., see Moroder et al. (2009) or Ramu et al. (2009)). The detailed structural characterization of the interaction is laborious and time consuming, and although revealing the three-dimensional details of antibiotic-ribosome binding can be helpful in combination with modern computational methods to find new potential leads (Wimberly, 2009), such structure-based drug design (SBDD) is not always successful. Moreover, SBDD usually relates very close to the original scaffold and location of ribosome interaction. A different, functionally driven approach has been chosen by Starosta et al. (2009). The authors have focused on one class of antibiotics, namely thiopeptides, which are remarkable natural products with thiostrepton as the flagship member. The structural complexity and biological properties have made thiopeptides one of the most attractive targets for chemists engaged in total synthesis (Nicolaou and Montagnon, 2008). Starosta et al. (2009) have recognized the potential of thiopeptide-based fragment libraries derived from retrosynthetic analysis of thiopeptides. Together with their synthetic chemistry colleague David Chen, the authors set out to validate the potential of these fragments as novel antibiotic scaffolds by establishing three functional assays (Figure 1). All three assays represent in vitro ribosomal set-ups that address distinct steps of translation; these involve: (i) monitoring of 30S initiation complex (30SIC) versus 70S initiation complex (70SIC) formation by a fluorescently labeled IF2 derivative, (ii) monitoring of GTPase activity either via colorimetric detection of inorganic phosphate formation or detection of inorganic phosphate binding to a fluorescent derivative of phosphate-binding protein, and (iii) monitoring of GFP production in a coupled transcription and translation system. Based on these assays, the authors screened separate fragment libraries of thiostrepton, nosiheptide, micrococcin, and GE2270A/T antibiotics. The promising outcome of the high-throughput study was the identification of four distinct families of thiopeptide precursor compounds with significant inhibitory properties and/or competitive inhibitory effects to their related full-size antibiotics (for further details, see Starosta et al. (2009)).

The urgent need for efficient functional assays for lead compound identification is not only reflected by the present work. Along these lines, another novel tool for analyzing antibiotic interaction has been described by Mankin and coworkers very recently (Llano-Sotelo et al., 2009). Their assay relies on ribosomes that carry a site-specific fluorescent label covalently attached to one of the ribosomal proteins. Moreover, the efforts of pharmaceutical companies on ribosome-based screenings to identify novel antibiotics have been reported on tracking bacterial tRNA synthetase activity using an *E. coli* S30-based transcription and translation assay (Dermyer et al., 2007). High-throughput screening assays for inhibition of elongation factor P and ribosomal peptidyl transferase activity using *Staphylococcus aureus* EF-P and a reconstituted *E. coli* ribosomal system represent another recent example (Swaney et al., 2006).

The incidence of antibiotic resistance has made the discovery of new scaffolds to a primary goal in antibiotic research. Besides mining underexplored microbial niches for natural products, repurposing libraries of synthetic molecules by functionally driven assays that address their suspected molecular targets will contribute significantly to reach this aim.

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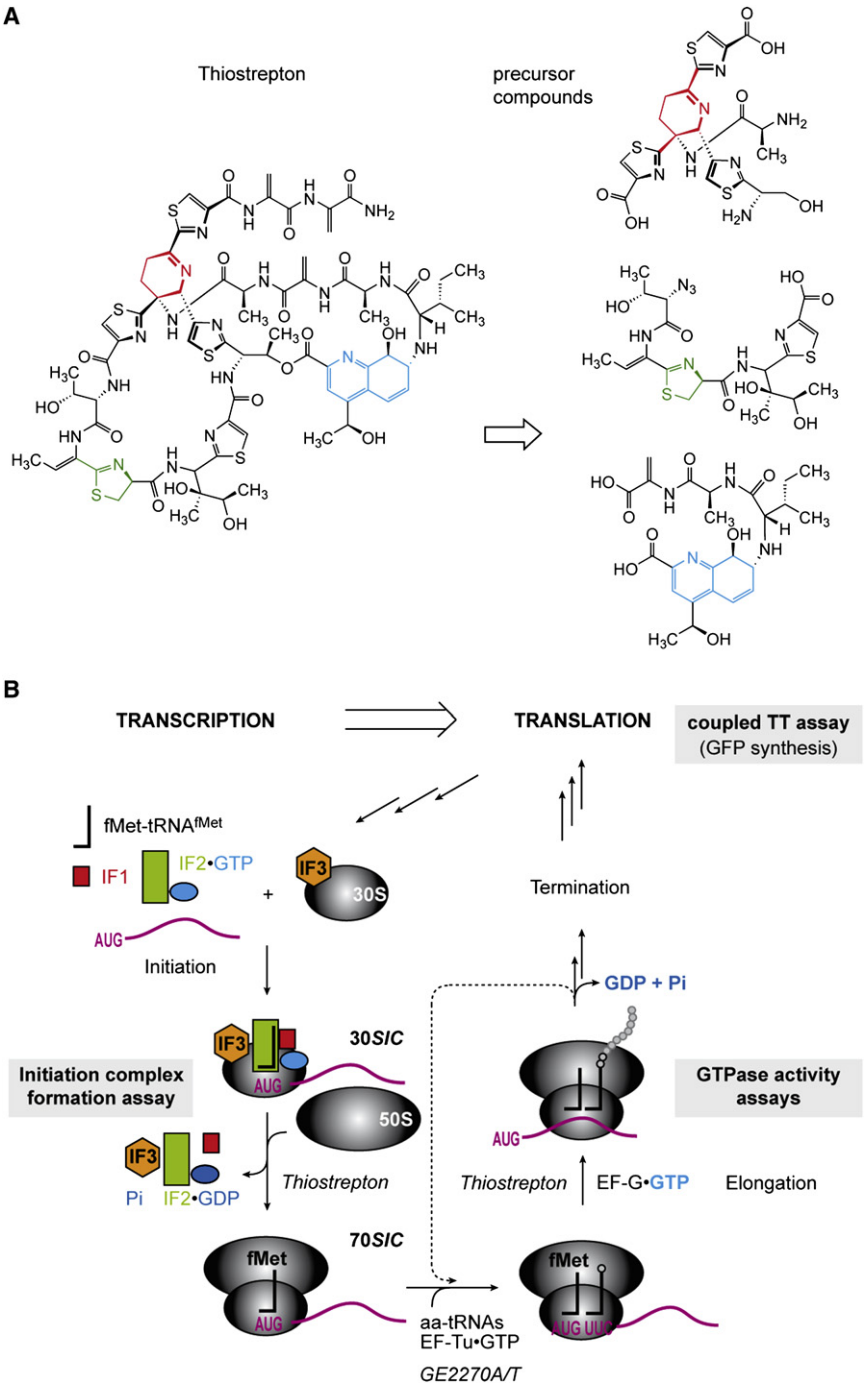

Figure 1. Identification of Lead Compounds Derived from Thiopeptide Antibiotics

(A) Thiostrepton is the most prominent member of the thiopeptide family, active against Gram-positive bacteria, and was used in veterinary medicine for many years. Structure of thiostrepton (left) and fragment compounds derived from retrosynthetic analysis (right).

(B) The urgent need for functional ribosomal assays in modern drug design is exemplified by Starosta et al. (2009) in a study published in this issue of *Chemistry & Biology*. They demonstrate the identification of thiopeptide fragments with inhibitory effects based on high-throughput ribosomal assays that target specific steps of the translation apparatus as indicated above.