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From the Structure and Function of the Ribosome to New Antibiotics

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We have obtained many insights into the structural basis of ribosome function in protein synthesis from our structural studies of the large ribosomal subunit as well as the 70S bacterial ribosome, and their complexes with substrates, protein factors or antibiotics. These have elucidated the mechanism by which this ribozyme catalyzes peptide bond formation and the specificity and mode of its inhibition by antibiotics.

During the process of protein synthesis elongation, the 70S ribosome is in various conformational states bound to various different ligands, and the structures of these functional states are beginning to emerge. Our structure of the 70S ribosome complexed with an mRNA, $tRNA^{fmet}$ in the P site and elongation factor P (EF-P), shows EF-P bond between the P site and the E site and interacting extensively with the P-site tRNA along its entire length. EF-P may be stimulating the initiation of the formation of the first peptide bond by stabilizing the $tRNA^{fmet}$ in the correct position. Our most recent structures of the 70S ribosome bound to either hibernation promoting factor or ribosome modulation factor show how these factors prevent the initiation of protein synthesis by blocking tRNA binding or interaction with the Shine-Dalgarno mRNA sequences. Protein synthesis by the ribosome can be regulated by numerous different nascent chain sequences and the binding of a small molecule ligand, resulting in polypeptide chain arrest. A Cryo-EM derived model of the 70S ribosome with a TnaC peptidyl-tRNA in the P site shows the polypeptide to be extended and ordered, making numerous interactions with the tunnel wall. Various strategies are being pursued to obtain high resolution crystal structures of the 70S ribosome containing arrested polypeptides in the tunnel.

The structures of some of our antibiotic complexes have been used by Rib-X Pharmaceuticals, Inc. of New Haven to develop new potential antibiotic compounds that are effective against MRSA, one of which has successfully completed phase II clinical trials. Recently, we have determined the crystal structures of the 70S ribosome bound to two compounds that are effective against tuberculosis, capreomycin and viomycin. Since their binding site is adjacent to those of two antibiotics that bind to the small subunit, the design of new anti-TB antibiotics by chemically combining components of the neighboring compounds should be possible.

Keywords: RNA structure, Ribosome, Antibiotic resistance

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Heterogeneity within Order in Metal-Organic Frameworks

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Metal-Organic Frameworks (MOFs) are a class of crystalline materials constructed by the linkage of inorganic units through organic molecules. During the past years the number of new compounds belonging to this family of materials has grown exponentially and MOFs are now considered as a new class of materials.

In order to rationalize the discovery of new MOFs, we have developed the reticular chemistry, where compounds with particular topologies can be prepared by the assembly of building units with specific geometries. This, for instance, allowed us to obtain materials with ultra-high porosity [1], and at the same time we have also demonstrated that these principles can be applied to compounds other than MOFs, like covalent organic frameworks (COFs) [2].

However, we also realize that the modular nature of MOFs offer a unique platform for the creation of new materials that have the intrinsic order of crystalline compounds and at the same time are able to display a higher degree of complexity.

Thus, we can prepare a MOF with a designed topology, *i.e.* **pcu**, and provided it with specific binding sites located at precise positions along the framework by using organic links that contains macrocycles. The resulting material displays the inherent properties of a MOF and is also capable of docking molecules in a specific manner [3].

We also show that MOFs can incorporate a large number of different functionalities on linking groups in a way that mixes the linker, rather than forming separate domains. Our strategy to make Multi-Variant (MTV) MOFs [4] is to assemble their structures from links with different functional groups whose orientation, number, relative position, and ratio along the backbone can be controlled by virtue of the unchanged length of the link and its unaltered connectivity. In this way, each of the pores within the MOF would have an array of functionalities pointing into its center.

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