

## Text Descriptions (Inputs)

In bacteria, the synthesis of the protective peptidoglycan sacculus is a dynamic process that is tightly regulated at multiple levels. Recently, the lipoprotein co-factor LpoB has been found essential for the in vivo function of the major peptidoglycan synthase PBP1b in Enterobacteriaceae. Here, we reveal the crystal structures of *Salmonella enterica* and *Escherichia coli* LpoB. The LpoB protein can be modeled as a ball and tether, consisting of a disordered N-terminal region followed by a compact globular C-terminal domain. Taken together, our structural data allow us to propose new insights into LpoB-mediated regulation of peptidoglycan synthesis.

The chromodomain of the HP1 family of proteins recognizes histone tails with specifically methylated lysines. Here, we present structural, energetic, and mutational analyses of the complex between the *Drosophila* HP1 chromodomain and the histone H3 tail with a methyllysine at residue 9, a modification associated with epigenetic silencing. The histone tail inserts as a beta strand, completing the beta-sandwich architecture of the chromodomain. The methylammonium group is caged by three aromatic side chains, whereas adjacent residues form discerning contacts with one face of the chromodomain. Comparison of dimethyl- and trimethyllysine-containing complexes suggests a role for cation- $\pi$  and van der Waals interactions, with trimethylation slightly improving the binding affinity.

The high-throughput docking protocol called ALTA-VS (anchor-based library tailoring approach for virtual screening) was developed in 2005 for the efficient in silico screening of large libraries of compounds by preselection of only those molecules that have optimal fragments (anchors) for the protein target. Here we present an updated version of ALTA-VS with a broader range of potential applications. The evaluation of binding energy makes use of a classical force field with implicit solvent in the continuum dielectric approximation. In about 2 days per protein target on a 96-core compute cluster (equipped with Xeon E3-1280 quad core processors at 2.5 GHz), the screening of a library of nearly 77 000 diverse molecules with the updated ALTA-VS protocol has resulted in the identification of 19, 3, 3, and 2  $\mu\text{M}$  inhibitors of the human bromodomains ATAD2, BAZ2B, BRD4(1), and CREBBP, respectively. The success ratio (i.e., number of actives in a competition binding assay in vitro divided by the number of compounds tested) ranges from 8% to 13% in dose-response measurements. The poses predicted by fragment-based docking for the three ligands of the BAZ2B bromodomain were confirmed by protein X-ray crystallography.

## Protein Designs (Outputs)

