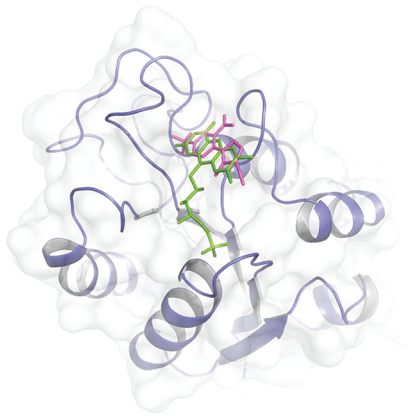
In this ISSUE

A New Flavor of Antibiotic

Helicobacter pylori (Hp) is a pathogenic bacteria that likes to take up residence in the gastrointestinal tract of humans. In fact, over half of the world's population is infected with Hp, and while many people are asymptomatic, the pathogen can cause various gastrointestinal disorders including gastritis and ulcers and has also been linked to some stomach cancers. Increasing resistance of Hp to broad spectrum antibiotics, coupled with challenges in developing an effective anti-Hp vaccine, speak to the need for inexpensive, effective new drugs against the bug. To this end, Cremades *et al.* (DOI: 10.1021/cb900166q) describe the development of a high throughput screen for identifying small molecules that target the Hp protein flavodoxin.

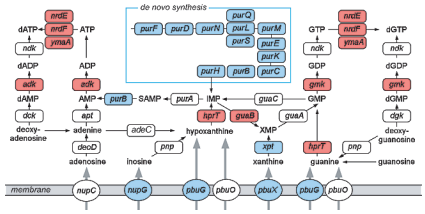
Flavodoxin is part of a metabolic pathway in Hp that is essential for survival. Structural studies reveal a unique pocket in Hp flavodoxin that suggests it as a promising target for the development of selective inhibitors. Indeed, screening of 10,000 small molecules led to the identification of three compounds that specifically inhibited flavodoxin function, selectively killed the bacteria over human cells, and were not toxic when orally administered to mice.



Switching to Riboswitches for Antibiotic Design

Though proteins are most often thought of as the regulators of gene expression, RNA elements called riboswitches have recently been implicated in controlling the production of small molecules to which they selectively bind. Riboswitches typically reside in the 5′ untranslated regions of bacterial mRNAs, and their involvement in key metabolic pathways suggests their potential as drug targets for some pathogenic bacteria. Kim *et al.* (DOI: 10.1021/cb900146k) present the design, synthesis, and activity of small molecule inhibitors of a guanine riboswitch from the bacteria *Bacillus subtilis*.

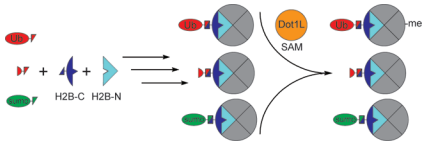
The crystal structure of the riboswitch was used to guide the design of 16 guanine analogs capable of binding to it. The compounds were tested for riboswitch binding, antibacterial activity, and their mechanism of action. One compound that inhibited bacterial growth was also found to strongly repress reporter gene expression under the control of a guanine riboswitch. The results offer compelling evidence that inhibition of riboswitch activity is a viable strategy for novel antibiotic design and that riboswitch structure is a valid starting point for inhibitor design.



Semisynthetic Histones

Histones, the main protein components of chromatin, are decorated with a multitude of posttranslational modifications, such as ubiquitylation, methylation, and acetylation, which orchestrate their regulatory role in expression of the genome. Deciphering the mechanistic function of these modifications is a formidable task; access to homogeneous preparations of histones with defined modifications would greatly facilitate such investigations. Building on a previously developed method for the semisynthesis of ubiquitylated histone H2B (uH2B), McGinty *et al.* (DOI: 10.1021/cb9002255) report a high-yielding synthesis of a slightly modified uH2B and its use in the exploration of the cross-talk between H2B and histone 3 (H3).

Mutation of a glycine residue in H2B to an alanine facilitated the production of tens of milligrams of a uH2B referred to as uH2BG76A. This ubiquitylated H2B variant was used to investigate how uH2B promotes the methylation of histone H3 lysine 79 by a methyltransferase called Dot1L. Specifically, kinetic and structure−activity relationship experiments offered intriguing insights into an unexpected role of ubiquitin in the reaction.



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