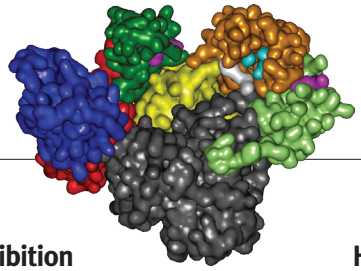
In this ISSUE

acs chemical biology



Alternative Inhibition

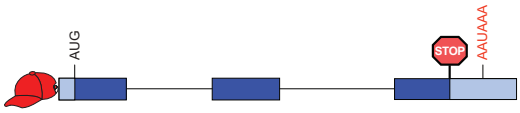
HIV relies on reverse transcriptase (RT) for replication, and this enzyme is a central drug target in the fight against AIDS). RT also possesses ribonuclease H (RNase H) activity, and compounds that inhibit this activity could be valuable additions to the medicine cabinet of AIDS drugs. Wendeler *et al.* (p 635) report the discovery of two vinylogous ureas that potently and selectively inhibit the RT RNase H activity of HIV-1 and HIV-2.

The two inhibitors were identified by screening libraries from the National Cancer Institute for RNase inhibition. Mass spectrometric protein footprinting and mutagenesis studies helped reveal that, unlike other RNase H inhibitors, the compounds target a binding pocket outside the catalytic center. This study highlights the potential of allosteric inhibitors in the design of novel AIDS drugs.

Alternative Polyadenylation

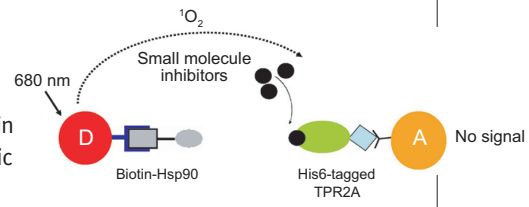
Of the many RNA processing mechanisms used to control gene expression, alternative polyadenylation is just beginning to be explored. Alternative polyadenylation refers to those pre-messenger RNAs that possess more than one polyadenylation signal, leading to generation of alternative RNA transcripts. These alternative transcripts could differ from their normally adenylated counterparts in their localization, stability, or transport or could code for entirely different proteins. Lutz (p 609) reviews our current understanding of alternative polyadenylation.

Insight into alternative polyadenylation has come from many areas of study. Discussed are the global genomic and bioinformatics studies that have revealed that over half of mammalian



genes are polyadenylated. In addition, tissue-specific studies have demonstrated that spatial, developmental, and functional needs can influence the polyadenylation process. Finally, exploration of alternative polyadenylation in viruses have provided clues about the role of RNA structure in polyadenylation signal choice.

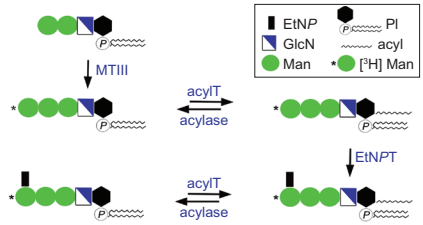
HOPping to New Cancer Drugs



The protein chaperone heat shock protein 90 (Hsp90) has been a hot research topic since its validation as a cancer target nearly a decade ago. Hsp90 helps proteins fold, especially proteins implicated in promoting cancer. Despite the promising anticancer activity of compounds that target the ATP binding site of Hsp90, poor solubility and toxic side effects threaten to limit their application. Now, Yi and Regan (p 645) describe the identification of a new class of Hsp90 inhibitors that function by a novel mechanism of action.

Hsp90 does not work in isolation, and the authors exploit the interaction between Hsp90 and another chaperone, Hsp organizing protein (HOP), in their examination of close to 100,000 compounds for novel Hsp90 inhibitors. A group of compounds containing a 7-azapteridine ring system was found to selectively kill cancer cells by disrupting the Hsp90–HOP interaction.

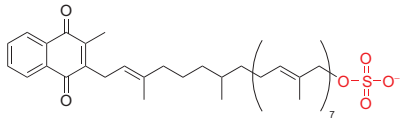
Putting *Trypanosoma brucei* to Sleep



Trypanosoma brucei is the causative agent of African sleeping sickness, a disease with poor treatment options that is responsible for ~50,000 deaths annually. Glycoproteins on the surface of *T. brucei* are anchored to the membrane by glycosylphosphatidylinositol (GPI), and disruption of GPI biosynthesis is a well-validated drug discovery strategy for the disease. Urbaniak *et al.* (p 625 and Point of View p 601) systematically probe the substrate recognition properties of various enzymes late in the GPI biosynthetic pathway of *T. brucei* in the search for new drug targets for this pathogen.

Several substrate analogs of the GPI enzyme mannosyltransferase III (MTIII) were synthesized and subsequently tested in a cell-free system recapitulating the trypanosomal GPI pathway. Structure–activity analysis revealed insightful mechanistic details about the pathway, as well as intriguing differences between the mammalian and trypanosomal MTIII that intimate its potential as a therapeutic target.

An Unequivocal Menaquinone



Given that a staggering one-third of the world's population is affected by tuberculosis (TB), insight into the pathogenicity of *Mycobacterium tuberculosis*, the causative agent of TB, is critical to developing effective strategies to combat the disease. S881 is a sulfated metabolite of *M. tuberculosis* that appears to attenuate its virulence, but its structure has remained a mystery in part because of its low abundance in lipid extracts. Toward exploring the intriguing biological activity of this metabolite, Holsclaw *et al.* (p 619) turn to mass spectrometry to elucidate its structure.

After anion exchange chromatography was used to enrich the lipid extracts for S881, high-resolution, high mass accuracy, and tandem mass spectrometry facilitated deduction of the structure of this elusive molecule. S881 is a previously undescribed sulfated derivative of dihydromenaquinone-9, the primary quinol electron carrier in *M. tuberculosis*.

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