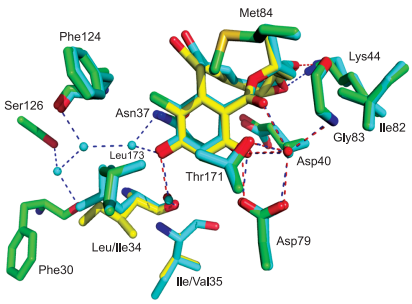
In this ISSUE

Resisting Hsp90 Resistance

Inhibitors of the protein chaperone heat shock protein 90 (Hsp90) are a promising new class of anticancer agents. These inhibitors cripple the ability of the protein to facilitate the folding and maturation of several key oncogenic proteins. Like ATP, the highly selective Hsp90 inhibitors geldanamycin (GdA) and radicicol (RAD) bind to the nucleotide binding site of Hsp90, suggesting that development of resistance to antibiotics might be limited due to the importance of the integrity of the binding site for Hsp90 function. However, close examination of the Hsp90 of the RAD-producing fungus *Humicola fuscoatra* enabled Prodromou *et al.* (DOI 10.1021/cb9000316) and Point of View (DOI 10.1021/cb9000712) to reveal how this organism produces an Hsp90 inherently resistant to RAD.

While the ATP-binding site of Hsp90 proteins is highly conserved across species, the *H. fuscoatra* Hsp90 contains a conservative change near the RAD binding site, an isoleucine in place of the normal leucine. Co-crystal structures indicated that this change causes an increase in hydration around RAD, which results in a decrease in affinity for RAD but not GdA or ATP. These findings offer intriguing insight into how resistance to Hsp90 inhibitors might emerge.



Ubiquitous Ubiquitination Enzymes

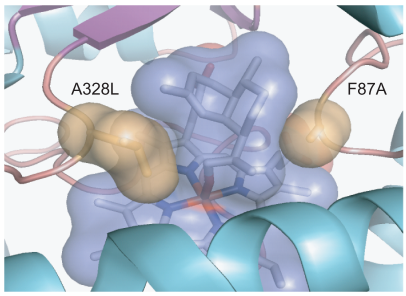
Modification of proteins with ubiquitin (Ub) is a critical component of protein regulation and provides instructions to the cell regarding trafficking or degradation. An intricate yet somewhat undefined network of enzymes controls Ub attachment to target proteins and removal from these proteins. Proteomic profiling of all of the proteins involved might contribute greatly to our understanding of this complex system and help in the design of small molecules capable of disrupting the system. To this end, Love *et al.* (DOI 10.1021/cb9000348) use activity-based protein profiling to search for additional enzymes involved in the ubiquitination system.

The profiling strategy is based on previous studies in which chemical ligation methods enabled installation of an electrophilic group at the C-terminus of an epitope-tagged Ub fusion protein. Redesign of the electrophilic group led to the creation of an expanded set of Ub-based chemical probes capable of tagging additional enzymes involved in ubiquitination. Several enzymes involved in all classes of Ub modification, including the Ub conjugating and ligation machinery as well as deubiquitinating enzymes, were uncovered in this effort.

Promiscuous Enzymes Battle Malaria

The plant natural product artemisinin is a promising drug for treatment of malaria, the potentially fatal, mosquito-borne disease that affects hundreds of millions of people annually. The limited supply from natural sources and high cost of synthetic preparations, however, preclude administration of this drug in many of the locations that need it the most. A key challenge in the semi-synthesis of artemisinin is the transformation of the terpene olefin precursor amorphadiene to dihydroartemisinic acid, which is the immediate precursor to artemisinin. Using an elegant combination of an enzymatic oxidation and highly selective synthetic chemistry, Dietrich *et al.* (DOI 10.1021/cb900006h) now present a highly efficient semi-biosynthetic route for the generation of dihydroartemisinic acid.

Conversion of artemisinin to dihydroartemisinic acid requires the selective oxidation of a terminal alkene group. Computer modeling guided the clever bioengineering of a cytochrome P450 monooxygenase into a substrate-promiscuous enzyme capable of converting this alkene group into an epoxide. Highly selective reduction and oxidation synthetic reactions led to generation of dihydroartemisinic acid.



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