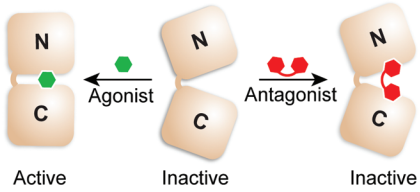
In this ISSUE

Trapping a "Venus Flytrap"

Not unlike the way the Venus flytrap captures its prey, bacterial receptors called periplasmic binding proteins (PBPs) undergo a dramatic conformational change in which two globular domains come together and essentially "trap" small molecule ligands upon binding. This conformational change leads to receptor activation, which triggers fundamental processes mediated by PBPs, including bacterial transport and chemotaxis. While many PBP agonists have been identified, PBP antagonists, which could be useful research tools and potential antimicrobial agents, have not been described. Borrok *et al.* (DOI: 10.1021/cb900021q) now report the discovery of a PBP antagonist and devise a general strategy for the creation of additional antagonists.

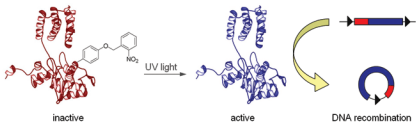
The *Escherichia coli* PBP glucose/galactose binding protein (GGBP) is activated by many glucose and galactose derivatives; some exceptions are those containing alkoxy substituents at the 3-position. This study reveals that the sugar 3-*O*-methyl-D-glucose does indeed bind to the receptor, but in a different orientation than GGBP agonists that does not enable the trap to close and thus prevents receptor activation. These insights facilitated the design of a novel dimeric glucose-containing GGBP antagonist.



An Enlightened Recombinase

Site-specific recombinase proteins are valuable tools for the manipulation of gene expression, facilitating various applications including gene induction, gene silencing, and the creation of gene knock-ins and knockouts. The popular Cre recombinase enzyme, which catalyzes DNA exchange between two conserved recognition sites, has been used extensively for such applications, but this system has proven difficult to control with high spatial and temporal accuracy. To tackle this limitation, Edwards *et al.* (DOI: 10.1021/cb900041s) have engineered a Cre recombinase that can be regulated with light.

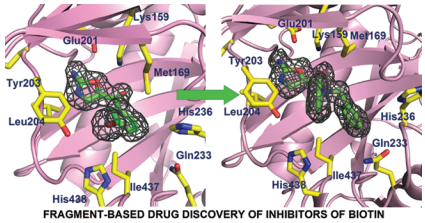
The investigators exploit the presence of a critical tyrosine in the active site of Cre to create an enzyme that functions only after exposure to light. Using unnatural amino acid mutagenesis, the active site tyrosine was replaced with a photocaged *o*-nitrobenzyl tyrosine (ONBY), which renders the enzyme inactive. Upon exposure to UVA light, the ONBY is converted to tyrosine, and enzymatic activity is restored. The ability to spatially and temporally control this light-activated system was demonstrated in DNA recombination experiments in bacteria and mammalian cells.



A Fragmented Approach

Although the recent emergence of various strains of drug-resistant bacteria has fueled large discovery efforts in search of new antibacterial agents, alarmingly no new antibiotics have been approved for human use in the postgenomic era. As many drug screening approaches have been designed for development of drugs targeted toward eukaryotic targets, alternate strategies that can be tailored to the unique aspects of bacterial targets and cell entry may facilitate the discovery process. Mochalkin *et al.* (DOI: 10.1021/cb9000102) now describe a fragment-based drug discovery approach in search of novel inhibitors of the bacterial drug target biotin carboxylase (BC).

Two complementary fragment-based approaches were used in the discovery effort. The first employed virtual screening methods to evaluate over 2 million compounds for their ability to bind to BC, followed by a biochemical assay to validate the most promising virtual hits. The second involved using the biochemical assay to screen a library of fragments, followed by Saturation Transfer Difference NMR methods to confirm inhibitor binding. These approaches led to the identification of a series of novel BC inhibitors.



FRAGMENT-BASED DRUG DISCOVERY OF INHIBITORS OF BIOTIN CARBOXYLASE FROM *E. COLI*.

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